10/706/999

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Patent Office
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I, JANENE PEISKER, TEAM LEADER EXAMINATION SUPPORT AND SALES hereby certify that annexed is a true copy of the Provisional specification in connection with Application No. 2002953602 for a patent by FUJISAWA PHARMACEUTICAL CO., LTD as filed on 30 December 2002.

WITNESS my hand this
Fourteenth day of November 2003

JANENE PEISKER
TEAM LEADER EXAMINATION
SUPPORT AND SALES

Regulation 3.2

Fujisawa Pharmaceutical Co., Ltd.

AUSTRALIA

Patents Act 1990

PROVISIONAL SPECIFICATION

for the invention entitled:

"New Compounds"

The invention is described in the following statement:

D E S C R I P T I O N

New compounds

Technical Field

This invention relates to new azole compounds having pharmacological activity, to a process for their production and to a pharmaceutical composition containing the same.

Background Art

The presence of two cyclooxygenase isoenzymes, cyclooxygenase-I (COX-I) and cyclooxygenase-II (COX-II) is known (Proc. Nat. Acad. Sci. USA 88, 2692-2696 (1991)).

Traditional non steroidal anti-inflammatory compounds (NSAIDs) have inhibiting activities of both COX-I and COX-II (J. Biol. Chem., 268, 6610-6614 (1993), etc). The therapeutic use thereof involves undesired effects on the gastrointestinal tract, such as bleeding, erosions, gastric and intestinal ulcers, etc.

It was reported that selective inhibition of COX-II shows anti-inflammatory and analgesic activities comparable with conventional NSAIDs but with a lower incidence of some gastrointestinal undesired effects (Pro. Nat. Acad. Sci. USA, 91, 3228-3232(1994)). Accordingly, various selective COX-II inhibitors have been prepared. However, it was reported that those "selective COX-II inhibitor" show some side-effects on kidney and/or insufficient efficacy on acute pains.

Further, some compounds such as SC-560, mofezolac, etc, which have certain selective inhibiting activity against COX-I. WO98/57910 shows some compounds having such activity. However, their selectivity of inhibiting COX -I does not seem to be enough to use them as a clinically acceptable and satisfactory analgesic agent due to their gastrointestinal disorders.

WO02/055502 shows some pyridine derivatives having cyclooxygenase inhibiting activity, particularly cyclooxygenase-I inhibiting activity. And WO99/51580 shows some

triazole derivatives having an inhibiting activity of cytokine production.

Disclosure of Invention

This invention relates to azole compounds, which have pharmaceutical activity such as cyclooxygenase (hereinafter described as COX) inhibiting activity, to a process for their production, to a pharmaceutical composition containing the same and to a use thereof.

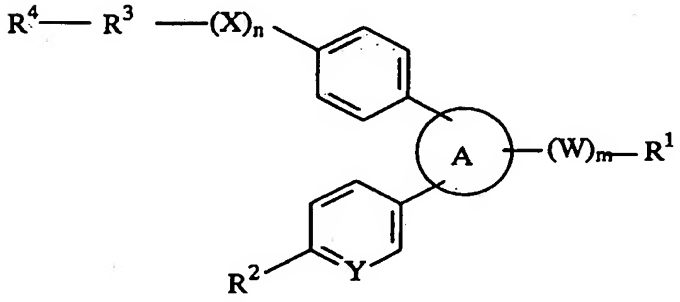
Accordingly, one object of this invention is to provide the azole compounds, which have a COX inhibiting activity.

Another object of this invention is to provide a process for production of the azole compounds.

A further object of this invention is to provide a pharmaceutical composition containing, as active ingredients, the azole compounds.

Still further object of this invention is to provide a use of the azole compounds for manufacturing a medicament for treating or preventing various diseases.

The new azole compounds of this invention can be represented by the following general formula (I):



(I)

wherein R^1 is lower alkyl which is optionally substituted with suitable substituent(s),
cyclo(lower)alkyl, lower alkynyl, cyano, acyl,
heterocyclic group, or
N,N-di(lower)alkylcarbamoyl;

R^2 is lower alkyl, lower alkoxy, cyano or 1H-pyrrol-1-yl;

R^3 is lower alkylene or lower alkenylene;

R^4 is hydroxy, protected hydroxy, amino, protected amino, carboxy, protected carboxy, acyl, or cyano;

X is O, S, SO or SO_2;

Y is CH or N;

W is O, S, SO or SO_2;

m is 0 or 1;

n is 0 or 1; and

is a N-containing heterocyclic group;

or salts thereof.

The object compound (I) of the present invention can be prepared by a similar manner to those of Preparations and/or Examples mentioned below.

The compounds of formula (I) may contain one or more asymmetric centers and thus they can exist as enantiomers or diastereoisomers. This invention includes both mixtures and separate individual isomers.

The compounds of the formula (I) may also exist in tautomeric forms and the invention includes both mixtures and separate individual tautomers.

The compounds of the formula (I) and its salts can be in a form of a solvate, which is included within the scope of the present invention. The solvate preferably include a hydrate and an ethanolate.

Also included in the scope of invention are radiolabelled derivatives of compounds of formula (I) which are suitable for biological studies.

In the above and subsequent description of the present specification, suitable examples of the various definitions to be included within the scope of the invention are explained in

detail in the following.

The term "lower" is intended to mean a group having 1 to 6 carbon atom(s), unless otherwise provided.

Suitable "lower alkyl", and lower alkyl moiety in the term "lower alkoxy" may be a straight or branched one, such as methyl, ethyl, propyl, isopropyl, butyl, isobutyl, tert-butyl, pentyl, hexyl or the like, in which preferable one is methyl or dimethyl.

Suitable lower alkoxy is methoxy, ethoxy, propoxy, isopropoxy, butoxy, isobutoxy, tert-butoxy, pentoxy, hexoxy, or the like, in which preferable one is methoxy.

Suitable "halogen" may be fluoro, chloro, bromo or iodo or the like, which preferable one is fluoro.

Suitable "lower alkyl substituted with halogen" may be lower alkyl substituted with one or more halogen atoms(s), such as fluoromethyl, difluoromethyl, trifluoromethyl, chloromethyl, dichloromethyl, trichloromethyl, bromomethyl, dibromomethyl, tribromomethyl, fluoroethyl, chloroethyl, 2,2,2-trifluoroethyl, 2,2,2-trichloroethyl, 2,2,3,3,3-pentafluoroethyl, fluoropropyl, fluorobutyl, fluorohexyl, or the like. And its preferable one is halogen-substituted C1-C2 alkyl. More preferable one is fluorine-substituted methyl, and most preferable one is trifluoromethyl or 2,2,2-trifluoroethyl.

Suitable "cyclo(lower)alkyl" may include 3 to 8-membered cycloalkyl such as cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl, cyclooctyl, and the like, preferably one having 5 to 7 carbon atoms.

Suitable "N,N-di(lower)alkylcarbamoyl" may be a carbamoyl group substituted with the same or different above lower alkyl groups on nitrogen atom, such as dimethylcarbamoyl, diethylcarbamoyl, dipropylcarbamoyl, diisopropylcarbamoyl, or the like. It is preferably di(C1-C4)carbamoyl, more preferably di(C1-C2 alkyl)carbamoyl.

Suitable alkynyl may be a monovalent branched or unbranched hydrocarbon radical containing at least one carbon-carbon triple bond, for example ethynyl, 2-propynyl, 2-butynyl, and the like.

Suitable salts of the compounds (I) are pharmaceutically acceptable conventional non-toxic salts and include a metal salt such as an alkali metal salt (e.g., sodium salt, potassium salt, etc.) and an alkaline earth metal salt (e.g., calcium salt, magnesium salt, etc.), an ammonium salt, an organic base salt (e.g., trimethylamine salt, triethylamine salt, pyridine salt, picoline salt, dicyclohexylamine salt, etc.), an organic acid salt (e.g., acetate, maleate, tartrate, methanesulfonate, benzenesulfonate, formate, toluenesulfonate, trifluoroacetate, etc.), an inorganic acid salt (e.g., hydrochloride, hydrobromide, sulfate, phosphate, etc.), a salt with an amino acid (e.g., arginine, aspartic acid, glutamic acid, etc.), or the like.

The processes for preparing the object compounds are explained in detail in the following.

In order to illustrate the usefulness of the object compounds (I), the pharmacological test data of the compounds (I) are shown in the following.

[A] ANALGESIC ACTIVITY:

Effect on adjuvant arthritis in rats:

(i) Test Method:

Arthritis was induced by injection of 0.5 mg of Mycobacterium tuberculosis (Difco Laboratories, Detroit, Mich.) in 50 μl of liquid paraffin into the right hind footpad of Lewis rats aged 7 weeks. Analgesic activity of a single dose of agents in arthritic rats was studied. Arthritic rats were randomized and grouped (n=10) for drug treatment based on pain threshold of left hind paws and body weight on day 22. Drugs (Test compounds) were administered and the pain threshold was measured 2hr after drug administration.

The intensity of hyperalgesia was assessed by the method of Randall - Selitto. The mechanical pain threshold of the left hind paw (uninjected hind paw) was determined by compressing the ankle joint with a balance pressure apparatus (Ugo Basile Co. Ltd., Varese, Italy). The threshold pressure of rats squeaking or struggling was expressed in grams. The threshold pressure of rats treated with drugs was compared with that of non-treated rats. A dose showing the ratio of 1.5 is considered to be the effective dose.

(ii) Test Results:

[B] Inhibiting activity against COX-I and COX-II (Whole Blood Assay):

(i) Test Method:

Whole blood assay for COX-I

Fresh blood was collected by syringe without anticoagulants from volunteers with consent. The subjects had no apparent inflammatory conditions and had not taken any medication for at least 7 days prior to blood collection. 500 μl aliquots of human whole blood were immediately incubated with 2 μl of either DMSO vehicle or a test compound at final concentrations for 1hr at 37C to allow the blood to clot. Appropriate treatments (no incubation) were used as blanks. At the end of the incubation, 5 μl of 250mM Indomethacin was added to stop the reaction. The blood was centrifuged at 6000 x g for 5min at 4C to obtain serum. A 100 μl aliquot of serum was mixed with 400 μl methanol for protein precipitation. The supernatant was obtained by centrifuging at 6000 x g for 5min at 4C and was assayed for TXB2 using an enzyme immunoassay kit according to the manufacturer's procedure. For a test compound, the results were expressed as percent inhibition of TXB2 production relative to control incubations containing DMSO vehicle. The data were analyzed by that a test compound at the indicated concentrations was changed log value and was applied simple linear regression. IC50 value was calculated by least squares method.

Whole blood assay for COX-II

Fresh blood was collected in heparinized tubes by syringe from volunteers with consent. The subjects had no apparent inflammatory conditions and had not taken any medication for at least 7 days prior to blood collection. 500 μl aliquots of human whole blood were incubated with either 2 μl DMSO vehicle or 2 μl of a test compound at final concentrations for 15min at 37C. This was followed by incubation of the blood with 10 μl of 5mg/ml lipopolysaccharide for 24hr at 37C for induction of COX-2. Appropriate PBS treatments (no LPS) were used as blanks. At the end of the incubation, the blood was centrifuged at 6000 x g for 5min at 4C to obtain plasma. A 100 μl aliquot of plasma was mixed with 400 μl methanol for protein precipitation. The supernatant was obtained by centrifuging at 6000 x g for 5min at 4C and was assayed for PGE2 using a radioimmunoassay kit after conversion of PGE2 to its methyl oximate derivative according to the manufacturer's procedure. For a test compound, the results were expressed as percent inhibition of PGE2 production relative to control incubations containing DMSO vehicle. The data were analyzed by that a test compound at the indicated concentrations was changed log value and was applied simple linear regression. IC50 value was calculated by least squares method.

(ii) Test Results:

Test Compound (Example No.)	COX-I IC50 (μM)	COX-II IC50 (μM)
70	< 0.01	> 0.1
71	< 0.01	> 0.1
214	< 0.01	> 0.1
216	< 0.01	> 0.1
332	< 0.01	> 0.1
334	< 0.01	> 0.1
335	< 0.01	> 0.1
336	< 0.01	> 0.1

It appeared, from the above-mentioned Test Results, that the compound (I) or pharmaceutically acceptable salts thereof of the present invention have an inhibiting activity against COX, particularly a selective inhibiting activity against COX-I.

[C] Inhibiting activity on aggregation of platelet

(i) Methods

Preparation of platelet-rich plasma

Blood from healthy human volunteers was collected into plastic vessels containing 3.8% sodium citrate (1/10 volume). The subject had no taken any compounds for at least seven days prior to blood collection. Platelet-rich plasma was obtained from the supernatant fraction of blood after centrifugation at 1200 r.p.m. for 10 min. Platelet-poor plasma was obtained by centrifugation of the remaining blood at 3000 r.p.m. for 10 min.

Measurement of platelet aggregation

Platelet aggregation was measured according to the turbidimetric method with an aggregometer (Hema Tracer). In the cuvette, platelet-rich plasma was pre-incubated for 2 min at 37C after the addition of compounds or vehicle. In order to quantify the inhibitory effects of each compound, the maximum increase in light transmission was determined from the aggregation curve for 7 min after the addition of agonist. We used collagen as agonist of platelet aggregation in this study. The final concentration of collagen was 0.5μg/mL. The effect of each compound was expressed as percentage inhibition agonist- induced platelet aggregation compared with vehicle treatment. Data are presented as the mean ± S.E.M. for six experiments. The IC_{50} value was obtained by linear regression, and is expressed as the compound concentration required to produce 50% inhibition of agonist-induced platelet aggregation in comparison to vehicle treatment.

It appeared, from the above-mentioned Test Result, that the compound (I) or pharmaceutically acceptable salts thereof of the present invention have an inhibiting activity against platelet

aggregation. Therefore, the compound (I) or pharmaceutically acceptable salts thereof are useful for preventing or treating disorders induced by platelet aggregation, such as thrombosis.

Additionally, it was further confirmed that the compounds (I) of the present invention lack undesired side-effects of non-selective NSAIDs, such as gastrointestinal disorders, bleeding, renal toxicity, cardiovascular affection, etc.

The object compound (I) or pharmaceutically acceptable salts thereof of this invention possesses COX inhibiting activity and possesses strong anti-inflammatory, antipyretic, analgesic, antithrombotic, anti-cancer activities, and so on.

The object compound (I) and pharmaceutically acceptable salt thereof, therefore, are useful for treating and/or preventing COX mediated diseases, inflammatory conditions, various pains, collagen diseases, autoimmune diseases, various immunological diseases, thrombosis, cancer and neurodegenerative diseases in human beings or animals by using administered systemically or topically.

More particularly, the object compound (I) and pharmaceutically acceptable salts thereof are useful for treating and/or preventing inflammation and acute or chronic pain in joint and muscle [e.g. rheumatoid arthritis, rheumatoid spondylitis, osteoarthritis, gouty arthritis, juvenile arthritis, scapulohumeral periarthritis, cervical syndrome, etc.];
lumbago;
inflammatory skin condition [e.g. sunburn, burns, eczema, dermatitis, etc.];
inflammatory eye condition [e.g. conjunctivitis, etc.];
lung disorder in which inflammation is involved [e.g. asthma, bronchitis, pigeon fancier's disease, farmer's lung, etc.];
condition of the gastrointestinal tract associated with inflammation [e.g. aphthous ulcer, Chrohn's disease, atopic gastritis, gastritis varialoforme, ulcerative colitis, coeliac disease, regional ileitis, irritable bowel syndrome, etc.];

gingivitis; menorrhalgia;
inflammation, pain and tumescence after operation or injury [pain after odontectomy, etc] ;
pyrexia, pain and other conditions associated with inflammation, particularly those in which lipoxygenase and cyclooxygenase products are a factor,
systemic lupus erythematosus, scleroderma, polymyositis, tendinitis, bursitis, periarteritis nodose, rheumatic fever, Sjogren's syndrome, Behcet disease, thyroiditis, type I diabetes, nephrotic syndrome, aplastic anemia, myasthenia gravis, uveitis contact dermatitis, psoriasis, Kawasaki disease, sarcoidosis, Hodgkin's disease, Alzheimers disease, or the like.

Additionally, the object compound (I) or a salt thereof is expected to be useful as therapeutical and/or preventive agents for cardiovascular or cerebrovascular diseases, the diseases caused by hyperglycemia and hyperlipemia.

The object compound (I) and a salt thereof can be used for prophylactic and therapeutic treatment of arterial thrombosis, arterial sclerosis, ischemic heart diseases[e.g. angina pectoris (e.g. stable angina pectoris, unstable angina pectoris including imminent infarction, etc.), myocardial infarction (e.g. acute myocardial infarction, etc.), coronary thrombosis, etc.], ischemic brain diseases [e.g. cerebral infarction (e.g. acute cerebral thrombosis, etc.), cerebral thrombosis (e.g. cerebral embolism, etc.), transient cerebral ischemia (e.g. transient ischemic attack, etc.), cerebrovascular spasm after cerebral hemorrhage(e.g. cerebrovascular spasm after subarachnoid hemorrhage, etc.), etc.], pulmonary vascular diseases (e.g. pulmonary thrombosis, pulmonary embolism etc.), peripheral circulatory disorder [e.g. arteriosclerosis obliterans, thromboangiitis obliterans (i.e. Buerger's disease), Raynaud's disease, complication of diabetes mellitus (e.g. diabetic angiopathy, diabetic neuropathy, etc.), phiebothrombosis (e.g. deep vein thrombosis, etc.), etc.],

complication of tumors (e.g. compression thrombosis), abortion [e.g. placental thrombosis, etc.],
restenosis and reocclusion [e.g. restenosis and/or reocclusion after percutaneous transluminal coronary angioplasty (PTCA), restenosis and reocclusion after the administration of thrombolytic drug (e.g. tissue plasminogen activator (TPA), etc.)],
thrombus formation in case of vascular surgery, valve replacement, extracorporeal circulation [e.g. surgery (e.g. open heart surgery, pump-oxygenator, etc.) hemodialysis, etc.] or transplantation, disseminated intravascular coagulation (DIC), thrombotic thrombocytopenia, essential thrombocytosis, inflammation (e.g. nephritis, etc.), immune diseases,
atrophic thrombosis, creeping thrombosis, dilation thrombosis, jumping thrombosis, mural thrombosis, etc.

The object compound (I) and a salt thereof can be used for the adjuvant therapy with thrombolytic drug (e.g. TPA, etc.) or anticoagulant (e.g. heparin, etc.).

And, the compound (I) is also useful for inhibition of thrombosis during extra corporeal circulation such as dialysis.

Particularly, the following diseases are exemplified: pains caused by or associated with rheumatoid arthritis, osteoarthritis, lumbar rheumatism, rheumatoid spondylitis, gouty arthritis, juvenile arthritis, etc; lumbago; cervico-omo-brachial syndrome; scapulohumeral periarthritis; pain and tumescence after operation or injury; etc.

For therapeutic purpose, the compound (I) and a pharmaceutically acceptable salt thereof of the present invention can be used in a form of pharmaceutical preparation containing one of said compounds as an active ingredient, in admixture with a pharmaceutically acceptable carrier such as an organic or inorganic solid or liquid excipient suitable for oral, parenteral or external administration. The pharmaceutical preparations may be capsules, tablets, dragees, granules, inhalant, suppositories, solution, lotion, suspension, emulsion, ointment, gel, or the like. If desired, there may be included in these preparations, auxiliary substances, stabilizing agents, wetting, or emulsifying agents, buffers and other commonly used additives.

While the dosage of therapeutically effective amount of the compound (I) will vary depending upon the age and condition of each individual patient, an average single dose of about 0.01 mg, 0.1 mg, 1 mg, 10 mg, 50 mg, 100 mg, 250 mg, 500 mg and 1000 mg of the compound (I) may be effective for treating the above-mentioned diseases. In general, amounts between 0.01 mg/body and about 1,000 mg/body may be administered per day.

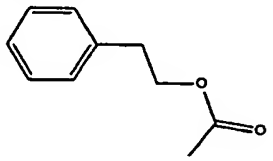
For therapeutic purpose, the analgesic agent of the present invention can be used in a form of pharmaceutical preparation suitable for oral, parenteral or external administration. The pharmaceutical preparations may be capsules, tablets, dragees, granules, inhalant, suppositories, solution, lotion, suspension, emulsion, ointment, gel, or the like.

Particularly, the analgesic agent of this invention is useful for treating or preventing acute or chronic pains associated with acute or chronic inflammations in human beings or animals by using administered systemically or topically.

The patents, patent applications and publications cited herein are incorporated by reference.

The following Preparations and Examples are given for the purpose of illustrating the present invention in detail.

Preparation 1

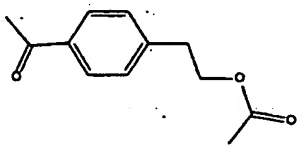


I

To a suspension of AlCl3 (45.9g) was added dropwise acetyl chloride (13.4ml) (About 5°C), and then I (25.7g) mentioned above under ice-cooling (5-10°C). After stirring for 8 hours, the reaction

(continued to the next page)

mixture was poured onto ice-water. The organic layer was separated and washed with water(twice) and 1NHCl, sat.NaHCO3 and brine, dried over MgSO4, filtered and evaporated under reduced pressure to give crude product. The product was distilled under reduced pressure to give 105.8g (84%) of the following compound (P0001)



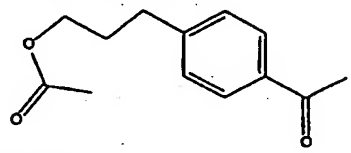
(P0001)

TLC Check: Ninhydrin/UV

b.p. 1> 91-117 °C /0.7mmHg. E111271-1 12.6g

2> 117 °C /0.7mmHg. E111271-2 105.8g

Preparation 2



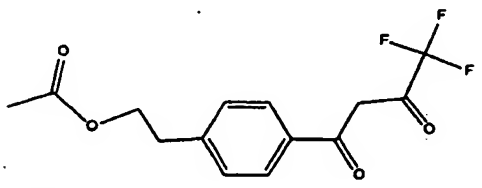
(P0002)

The above compound P0002 was prepared in a similar manner to that of P0001.

Mass (API-ES positive) : 243 (M+Na)+

200MHz 1H NMR (CDCl3, d) : 1.91-2.05(2H, m), 2.06(3H, s), 2.59(3H, s), 2.76(2H, t, J=7.7 Hz), 4.09(2H, t, J=6.5 Hz), 7.28(2H, d, J=8.2 Hz), 7.90(2H, d, J=8.2 Hz)

Preparation 3



(P0003)

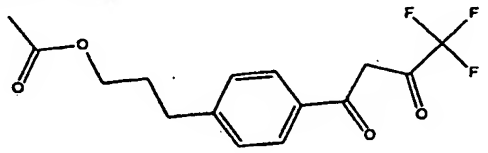
60% Sodium hydride 427mg was added to a solution of the compound P0001 (2g) and ethyl trifluoroacetate 2.6ml in DMF 10ml portionwise (in three portions) under ice bath cooling. The reaction mixture was stirred at same temperature for 45minutes. Then ice bath was replaced to water bath. The temperature of reaction mixture was raised to 24.5℃, then slowly fall down to 22℃ over 1hour. The mixture was stirred at r.t. for 1hour, then poured into a mixture of 1M HCl 12ml and ice 40ml. The whole mixture was extracted with AcOEt 20ml. The organic layer was washed with H2O 30ml, saturated aqueous sodium chloride solution, dried over magnesium sulfate, concentrated in vacuo. The residue was purified by silica gel column chromatography eluted with toluene. Obtained crystals were washed with chilled n-hexane 10ml and petroleum ether 5ml by decantation to give a compound P0003 as white crystals.

mp. 87-88℃

Mass (API-ES negative) : 301(M-H)+

200MHz 1H NMR (DMSO-d6, d) : 3.00(2H, t, J=6.7 Hz), 4.27(2H, t, J=6.7 Hz), 6.99(1H, s), 7.48(2H, d, J=8.3 Hz), 8.08(2H, d, J=8.3 Hz)

Preparation 4



(P0004)

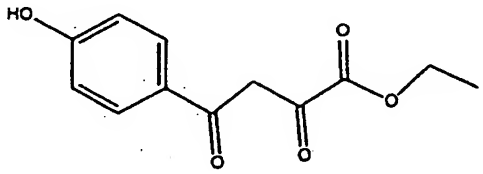
P0004 was prepared in a similar manner to that of P0003 as shown in Preparation 3.

Mass (API-ES negative) : 315 (M-H)+

NMR JA24.112

200MHz 1H NMR (CDCl3, d) : 1.92-2.06(2H, m), 2.06(3H, s), 2.74-2.82(2H, m), 4.10(2H, t, J=6.5 Hz), 6.55(1H, s), 7.33(2H, d, J=8.3 Hz), 7.89(2H, d, J=8.3 Hz)

Preparation 5



(P0005)

P0005 was prepared in a similar manner to that of P0003 as shown in Preparation 3.

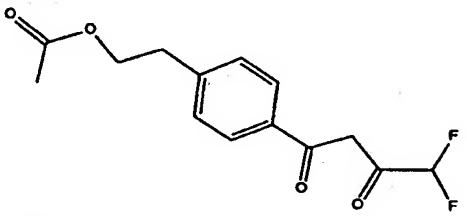
yellow crystals

Mass (API-ES positive) : 259 (M+Na)+

400MHz 1H NMR (CDCl3, d) :

1.41(3H, t, J=7.1 Hz), 4.40(2H, q, J=7.1 Hz), 6.93(2H, d, J=8.9 Hz), 7.02(1H, s), 7.96(2H, d, J=8.9 Hz)

Preparation 6

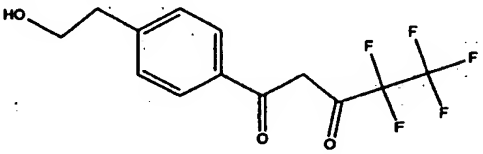


(P0006)

P0006 was obtained according to a similar manner to that of P0003.

(PREPARATION 3)

Preparation 7



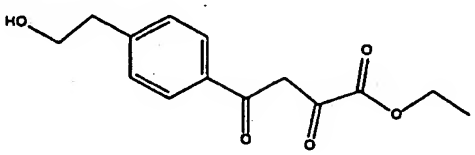
(P0007)

60% Sodium hydride 233mg was added to a solution of P0001 1g and ethyl pentafluoropropionate 0.93ml in three portions under ice bath cooling. The reaction mixture was stirred at 24-27℃ with cooling in a water bath for several hours, then poured into a mixture of ice and 1M HCl 50ml. The whole mixture was extracted with AcOEt twice. The combined organic layer was washed with saturated aqueous sodium chloride solution, dried over magnesium sulfate, and concentrated in vacuo to give P0007 1.94g as an oil.

Mass (API-ES negative) : 309 (M-H)+

200MHz 1H NMR (CDCl3, d) : 2.90-3.05(2H, m), 3.85-4.00(2H, m), 6.62(1H, s), 7.39(2H, d, J=8.3 Hz), 7.92(2H, d, J=8.3 Hz)

Preparation 8

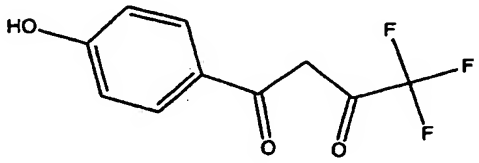


(P0008)

20% solution of sodium ethoxide in EtOH 18ml was added dropwise to a solution of P0001 (4.00g) and diethyl oxalate 5.95g in DMF 12ml at 4-6℃. After stirring at same temperature for 1hour, the reaction mixture was poured into a mixture of ice-water 100ml and conc.HCl 5ml,
and extracted with AcOEt. The organic layer was washed successively with 1M HCl, H2O, and saturated aqueous sodium chloride solution, dried over magnesium sulfate, treated with activated carbon, then filtered through a SiO2(20ml) pad. The pad was washed with AcOEt. The filtrate and combined washings were concentrated in vacuo to give P0008 (6.05g) as an oil.

Mass (API-ES positive) : 287(M+Na)+, (API-ES negative) 263(M-H)+
200MHz 1H NMR (CDCl3, d) : 1.42(3H, t, J=7.1Hz), 2.96(2H, t, J=6.5 Hz), 3.93(2H, t, J=6.5 Hz), 4.40(2H, q, J=7.1Hz), 7.06(1H, s), 7.38(2H, d, J=8.3 Hz), 7.96(2H, d, J=8.3Hz)

Preparation 9



(P0009)

To a solution of 4-Hydroxybenzophenone (160 g), Ethyl trifluoroacetate (182 ml), and ethanol (11 ml) in N,N-dimethylformamide (670 ml) was added portionwise sodium hydride (suspension in mineral oil, 103 g) over 15 minutes at 0 ~ 35℃. The mixture was stirring at room temperature for 2 hours, and then at 35 ~ 40℃ for 3 hours.

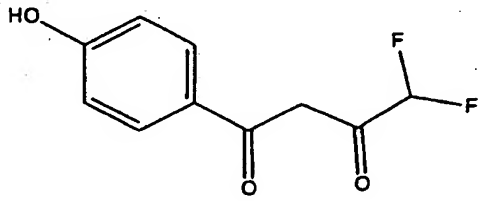
The mixture was poured into a mixture of ice and concentrated hydrogen chloride (320 ml) (aqueous layer total 4L) and diisopropyl ether (2 L). The aqueous layer was separated and extracted with diisopropyl ether (500 ml x 2). The combined organic layers were washed with water (500 ml x 4) and brine, dried over magnesium sulfate, and evaporated to give 415 g of solid.

The solid was dissolved in diisopropyl ether (200 ml) at 65℃. The solution was added dropwise hexane (1.5 L) under stirring at room temperature. After stirring at room temperature for 1 hour, The suspension was filtered and dried under reduced pressure to give solid (first crop, 109.53 g, 40%). The mother liquid evaporated and similarly treated diisopropyl ether (20 ml) and hexane (250 ml) to give second crop (71.11 g, 26%). P0009 (first corp and second corp total, 66.2%).

NMR(CDCl3); 5.65(1H, brs), 6.50(1H, s), 6.94(2H, d, J=8.8 Hz), 7.91(2H, d, J=8.8 Hz).

MS(ESI+), 255.1(M+Na)+.

Preparation 10



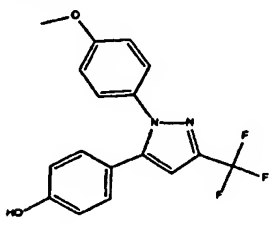
(P0010)

This compound was obtained according to a similar manner to that of P0009 (S0203744) as a powder (56.195 g, 102%).

NMR(CDCl3); 6.01(1H, t, J=54 Hz), 6.49(1H, s), 6.92(2H, d, J=8.8 Hz), 7.90(2H, d, J=8.8 Hz).

MS(ESI-), 213.3(M-H)+

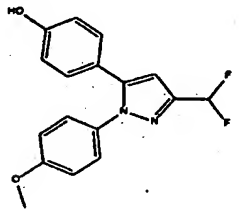
Preparation 11



(P0011)

A mixture of P0009 (100 g), 4-Methoxyphenylhydrazine hydrochloride (82.4 g), and sodium acetate (42.6 g) in acetic acid (550 ml) was stirring at 70℃ for 3 hours. After cooling to room temperature, the mixture was poured into water (4 L) and stirred at room temperature for 1 hour. The precipitate was filtered, washed with water (250 ml x 3) and Hex(500 ml x 2)、and dried at room temperature overnight to give powder (157.86 g)
The powder was purified by recrystallization from ethyl acetate and hexane to give P0011 as a powder 121.34G (77%).
NMR(CDCl3); 3.82(3H, s), 5.08(1H, brs), 6.67(1H, s), 6.77(2H, d, J=8.6Hz), 6.87(2H, d, J=9.0Hz), 7.09(2H, d, J=8.6Hz), 7.23(2H, d, J=9.0 Hz).
MS(ESI+); 357.1(M+Na)+.

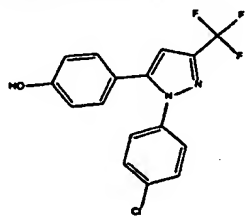
Preparation 12



(P0012)

This compound was obtained according to a similar manner to that of P0011 as a solid (3.2028 g, 72%).
NMR(DMSO-d6); 3.88(3H, s), 6.74(2H, d, J=8.6 Hz), 6.82(1H, s), 6.90(1H, d, J=8.6 Hz), 7.10(2H, d, J=8.6 Hz), 7.09(1H, t, J=55 Hz), 7.68(1H, dd, J=8.6, 2.7 Hz), 8.12(1H, d, J=2.7 Hz).
MS(ESI+); 316.1(M-H)+, 633.3(2M-H).

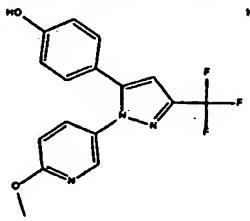
Preparation 13



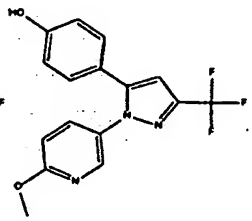
(P0013)

This compound was obtained according to a similar manner to that of P0011.

Preparation 14



(P0014)



(P0014-1)

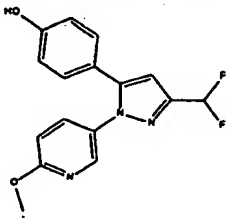
To a solution of P0014-1 (3.43 g) in water (7.7 ml) was added a solution of P0009 in acetic acid (50 ml). The mixture was then allowed to stand at room temperature overnight.

The mixture was poured into water (500 ml) and stirred at room temperature for 1 hour. The precipitate was filtered, washed with water (100 ml), and dried at room temperature to give P0014 as a brown solid (3.26 g, 90%).

NMR(DMSO-d6); 3.88(3H, s), 6.75(2H, d, J=8.6 Hz), 6.92(1H, d, J=8.5 Hz), 7.06-7.15(3H, m), 7.73(1H, dd, J=8.5, 2.8 Hz), 8.16(1H, d, J=2.8 Hz), 9.86(1H, s, OH).

MS(ESI-); 334.1(M-H)+, 669.2(2M-1)+.

Preparation 15



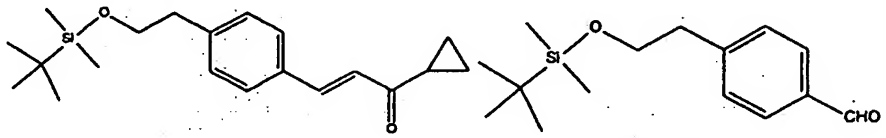
(P0015)

This compound was obtained according to a similar manner to that of P0014 as a pale brown powder (13.58 g, 91.7%).

NMR(DMSO-d6); 3.94(3H, s), 6.67(1H, s), 6.75(1H, t, J=55 Hz), 6.73-6.80(3H, m), 7.09(2H, d, J=8.6 Hz), 7.57(1H, dd, J=8.6, 2.6 Hz), 8.07(1H, d, J=2.6 Hz).

MS(ESI-); 316.1(M-H), 633.3(2M-H).

Preparation 16



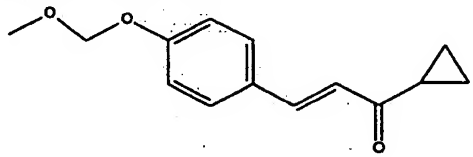
(P0016) (P0016-1)

1M NaOH 1ml was added to a solution of P0016-1 (reported in WO9427973) 1.31g and in EtOH 5ml and the mixture was stirred at amibient temperature overnight. The mixture partitioned between AcOEt and H2O. The organic layer was washed with H2O, saturated aqueous sodium chloride solution, dried over magnesium sulfate, and concentrated in vacuo. The residue was purified by silica gel column chromatography eluted with AcOEt / n-hexane to give P0016 (900mg) as an oil.

Mass (ESI+) : 331 (M+H)+

200MHz 1H NMR (DMSO-d6, d) : -0.05(6H, s), 0.82(9H, s), 0.94(4H, d, J=6.0 Hz), 2.38-2.52(1H, m), 2.78(2H, t, J=6.6 Hz), 3.79(2H, t, J=6.6Hz), 7.01(1H, d, J=16.2Hz), 7.29(2H, d, J=8.1Hz), 7.65(2H, d, J=8.1 Hz), 7.65(1H, d, J=16.2 Hz)

Preparation 17



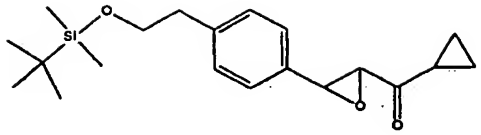
(P0017)

P0017 6.41g was prepared in a similar manner to that of P0016.

Mass (API-ES positive) : 255 (M+Na)+

200MHz 1H NMR (CDCl3, d) : 0.90-1.01(2H, m), 1.11-1.20(2H, m), 2.22(1H, m), 3.49(3H, s), 5.21(2H, s), 6.78(1H, d, J=16.0 Hz), 7.05(2H, d, J=8.7 Hz), 7.52(2H, d, J=8.7 Hz), 7.58(1H, d, J=16.0 Hz)

Preparation 18



(P0018)

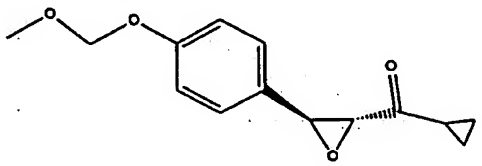
30% H2O2 0.64ml and 3M NaOH 0.64ml was added to a 0.25M solution of P0016 1.03g in EtOH:acetone=3:1. The mixture was stirred at ambient temperature overnight. The mixture was concentrated in vacuo, and partitioned between AcOEt and H2O. The organic layer was washed with H2O, saturated aqueous sodium chloride solution, dried over magnesium sulfate, and concentrated in vacuo to give P0018 (792mg) as an oil.

Mass (ESI+) : 347 (M+H)+

200MHz 1H NMR (DMSO-d6, d) :

-0.05(6H, s), 0.82(9H, s), 0.92-1.04(4H, m), 2.24(1H, m), 2.75(2H, t, J=6.7 Hz), 3.76(2H, t, J=6.7 Hz), 3.86(1H, d, J=1.9 Hz), 4.19(1H, d, J=1.9 Hz), 7.24(2H, d, J=8.4 Hz), 7.30(2H, d, J=8.4 Hz)

Preparation 19



(P0019)

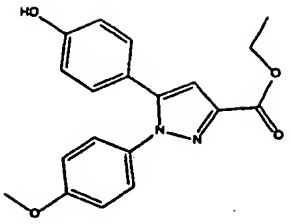
P0019 1.082g was prepared from P0017 1.0g in a similar manner to that of P0018.

Mass (API-ES positive) : 271(M+Na)+

200MHz 1H NMR (DMSO-d6, d) : 0.90-1.04(4H, m), 2.24(1H, m), 3.37(3H, s), 3.88(1H, d, J=1.9 Hz), 4.17(1H, d, J=1.9 Hz), 5.20(2H, s), 7.03(2H, d, J=8.7 Hz), 7.32(2H, d, J=8.7 Hz)

200MHz 1H NMR (CDCl3, d) : 0.90-1.07(2H, m), 1.12-1.26(2H, m), 2.18(1H, m), 3.48(3H, s), 3.58(1H, d, J=1.9 Hz), 4.05(1H, d, J=1.9 Hz), 5.18(2H, s), 7.04(2H, d, J=8.7 Hz), 7.23(2H, d, J=8.7 Hz)

Preparation 20



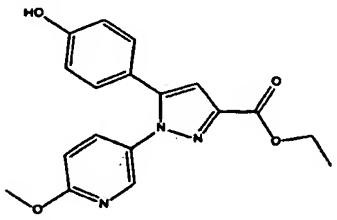
(P0020)

P0005 17.00g was dissolved in warm EtOH 68ml and AcOH 170ml at 70℃. To this solution was added P0005, suspended in H2O 20ml, in one portion. The mixture was stirred at 70℃ for 1.5hours and then poured into a mixture of ice 500ml and conc.HCl 10ml. Diisopropyl ether 100ml was added and the mixture was stirred at ambient temperature for 20minutes. The precipitates were collected and washed successively with 1M HCl, H2O, and diisopropylether. This was air dried overnight to give P0020 21.28g was a pale yellow powder.

Mass (ESI+) : 339 (M+H)+

400MHz 1H NMR (CDCl3, d) : 1.41(3H, t, J=7.1 Hz), 3.82(3H, s), 4.44(2H, q, J=7.1 Hz), 6.76(2H, d, J=8.7 Hz), 6.85(2H, d, J=9.0 Hz), 6.96(1H, s), 7.08(2H, d, J=8.7 Hz), 7.24(2H, d, J=9.0 Hz)

Preparation 21



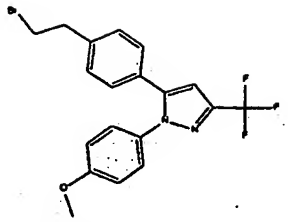
(P0021)

P0021 was prepared from P0005 in a similar manner to that of P0020. white powder

Mass (ESI+) : 340 (M+H)+

200MHz 1H NMR (DMSO-d6, d) : 1.31(3H, t, J=7.1 Hz), 3.88(3H, s), 4.32(2H, q, J=7.1 Hz), 6.74(2H, d, J=8.6 Hz), 6.92(1H, d, J=8.8 Hz), 7.00(1H, s), 7.09(2H, d, J=8.6 Hz), 7.71(1H, dd, J=8.8,2.7 Hz), 8.13(1H, d, J=2.7 Hz), 9.82(1H, s)

Preparation 22



(P0022)

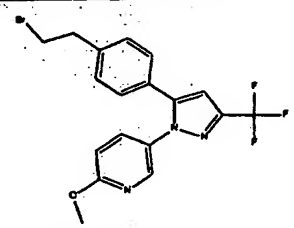
A solution of triphenylphosphine 831mg in THF 5ml was added dropwise to a solution of FR265158 521.8mg and carbon tetrabromide 1.15g in THF 5ml at ambient temperature. The reacion mixture was stirred at ambient temperaturer for 1hour. Carbon tetrabromide 573mg and triphenylphosphine 415mg were added in one portion and stirred for further 1hour. Unsoluble matter was filtered off and washed with THF. The filtrate and combined washings were concentrated in vacuo. The residue was purified by silica gel column chromatography eluted with AcOEt / n-hexane = 5%, then 25% to give P0022 647.2mg as pale yellow wax.

mp.60-70℃

Mass (API-ES positive) : 425,427 (M+H)+ , 447,449(M+Na)+

200MHz 1H NMR (CDCl3, d) : 3.12-3.19(2H, m), 3.52-3.60(2H, m), 3.82(3H, s), 6.72(1H, s), 6.87(2H, d, J=9.0 Hz), 7.16-7.30(6H, m)

Preparation 23



(P0023)

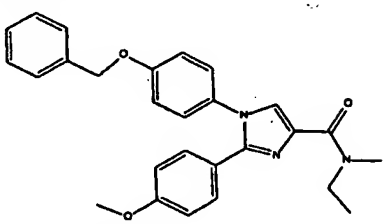
P0023 was prepared in a similar manner to that of P0022.

colorless oil

Mass (API-ES positive) : 448,450 (M+Na)+

400MHz 1H NMR (DMSO-d6, d) : 3.14(2H, t, J=7.2 Hz), 3.74(2H, t, J=7.2Hz), 3.88(3H, s), 6.92(1H, d, J=8.8Hz), 7.20(1H, s), 7.27(2H, d, J=8.4 Hz), 7.32(2H, d, J=8.4 Hz), 7.76(1H, dd, J=2.7,8.8 Hz), 8.19(1H, d, J=2.7 Hz),

Preparation 24



(P0024)

A mixture of I (0.44 g), N-ethylmethylamine (118 ml),1-hydroxybenzotriazole (186 mg) and 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (263 mg) in N,N-dimethylformamide (5 ml) was stirred at room temperature for overnight. The reaction mixture was poured into water and extracted with ethyl acetate, dried over MgSO4 and evaporated in vacuo. The residue was purified by column chromatography silica-gel eluting with (n-Hexane:AcOEt=1:1). The resulting precipitates were corrected by filtration and washed with diisopropyl ether to give P0024 (0.44 g).

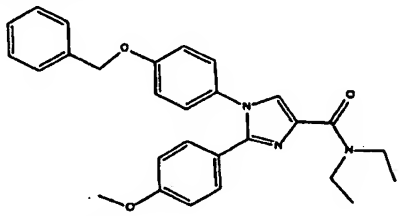
m.p. 118-119℃

NMR (DMSO-d6) d; 1.06-1.28 (3H, m), 2.91-3.02 (2H, m), 3.40-3.54 (2H, m), 3.74 (3H, s), 3.93-4.07 (1H, m), 5.15 (2H, s), 6.88 (2H, d, J=8.8Hz), 7.10 (2H, d, J=8.9Hz), 7.24-7.30 (4H, m), 7.36-7.49 (5H, m), 7.73 (1H, s).

IR (KBr): 3124, 3066, 2958, 2935, 2839, 1608 cm-1.

Mass m/e : 442 (M++1).

Preparation 25



(P0025)

P0025 was obtained in the similar manner that of P0024.

m.p.146-147℃

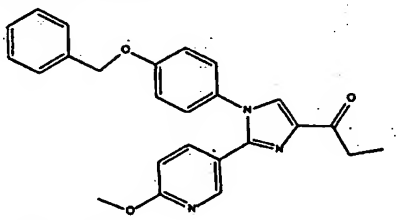
NMR (DMSO-d6) d; 1.10-1.30 (6H, m), 3.38-3.50 (2H, m), 3.74 (3H,

s), 3.85-4.02 (2H, m), 5.15 (2H, s), 6.88 (2H, d, J=8.8Hz), 7.10 (2H, d, J=8.9Hz), 7.24-7.30 (4H, m), 7.36-7.49 (5H, m), 7.72 (1H, s).

IR (KBr): 3113, 2972, 22929, 1593 cm-1.

Mass m/e : 456 (M++1).

Preparation 26



(P0026)

1N solution of ethylmagunesium bromide in tetrahydrofuran (8.63 ml) was added to a solution of FR270230 (1.1 g) in tetrahydrofuran (10 ml) under stirring at 0℃. After stirring at room temperature for 1 hour, the reaction mixture was poured into aqueous 10% potassium hydrogen sulfate and stirred at room temperature for 30 minutes. The mixture was alkalinised with saturated aqueous sodium hydrogen carbonate and extracted with ethyl acetate, washed with H2O, dried over MgSO4 and evaporated in vacuo. The resulting precipitates were collected by filtration and washed with diisopropyl ether to give P0026 (1.07 g).

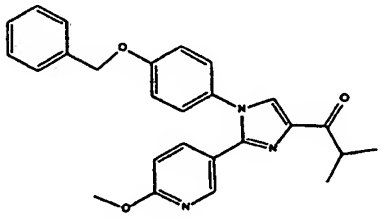
m.p. 126-128 ℃

NMR (DMSO-d6) d; 1.10 (3H, t, J=7.4Hz), 2.95 (2H, q, J=7.4Hz), 3.84 (3H, s), 5.16 (2H, s), 6.81 (1H, d, J=8.6Hz), 7.12 (2H, d, J=8.9Hz), 7.32-7.49 (7H, m), 7.66 (1H, dd, J=8.6Hz, 2.4Hz), 8.08 (1H, d, J=2.4Hz), 8.17 (1H, s).

IR (KBr): 3217, 3126, 3066, 3030, 2972, 2939, 2883, 1666, 1610 cm-1.

Mass m/e : 414 (M++1).

Preparation 27



(P0027)

P0027 (1.04 g) was obtained in the similar manner that of P0026.

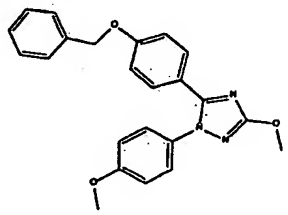
m.p. 118-120 ℃

NMR (DMSO-d6) d; 1.14 (6H,d, J=6.8Hz), 3.56-3.70(1H, m), 3.84 (3H, s), 5.16 (2H, s), 6.81 (1H, d, J=8.5Hz), 7.13 (2H, dd, J=9.1Hz, 2.3Hz), 7.32-7.49 (7H, m), 7.67 (1H, dd, J=8.5Hz, 2.4Hz), 8.08 (1H, d, J=2.4Hz), 8.19 (1H, s).

IR (KBr): 3126, 3064, 3033, 2968, 2875, 1660, 1608 cm-1.

Mass m/e : 428 (M++1).

Preparation 28



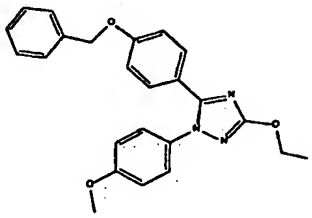
(P0028)

A mixture of P0047 (2 g, 5.36 mmol), potassium carbonate (2.22 g, 16.1 mmol) and dimethyl sulfate (0.711 ml, 7.5 mmol) in dimethylformamide (15 ml) was stirred at roomtemperature for 1.5 hours. The mixture was quenched with water and extracted with ethyl acetate. The organic layer was washed with water and brine, dried over magnesium sulfate, and evaporated to give crude solid. The solid was purified with column chromatography (SiO2 50 g, eluted with toluene:ethyl acetate =4:1). The desired P0028 was washed with isopropylether, isolated by filtartion, and dried in vacuo (1.02 g, 49.2% yield).

1H NMR (CDCl3, ppm) d 3.84(3H, s), 4.04(3H, s), 5.05(2H, s), 6.82-7.00(4H, m), 7.27-7.55(9H, m),

MS (ESI, m/e) 388(M+1)

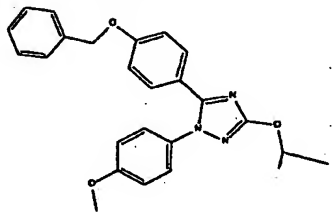
Preparation 29



(P0029)

P0029 was obtained according to a similar manner to that of P0028. 1H NMR (CDCl3, ppm) d 1.45(3H, t, J=7.0 Hz), 3.84(3H, s), 4.39(2H, q, J=7.0 Hz), 5.05(2H, s), 6.82-6.98(4H, m), 7.20-7.50(9H, m), MS (ESI, m/e) 402(M+1)

Preparation 30

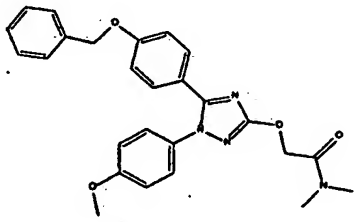


(P0030)

A mixture of P0047 (1 g, 2.68 mmol), potassium carbonate (1.11 g, 8.03 mmol) and isopropyl iodide (1.34 ml, 13.4 mmol) in dimethylformamide (5 ml) was stirred at 100°C for 2 hours. The mixture was quenched with water and extracted with ethyl acetate. The organic layer was washed with water and brine, dried over magnesium sulfate, and evaporated to give crude solid. The solid was purified with column chromatography (SiO2 50 g, eluted with toluene:ethyl acetate =5:1) (1.02 g, 49.2% yield).

1H NMR (CDCl3, ppm) d 1.43(6H, d, J=6.2 Hz), 3.84(3H, s), 4.92-5.12(4H, m), 6.81-7.00(4H, m), 7.20-7.52(9H, m),
MS (ESI, m/e) 416(M+1)

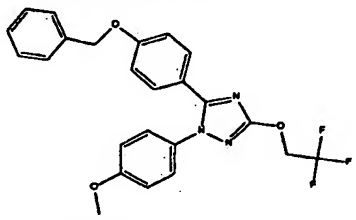
Preparation 31



(P0031)

P0031 was obtained according to a similar manner to that of P0030.
1H NMR (DMSO-d6, ppm) d 2.84(3H, s), 2.91(3H, s), 3.80(3H, s), 5.00(2H, s), 5.10(2H, s), 7.02(4H, d, J=8.9 Hz), 7.21-7.50(9H, m),
MS (ESI, m/e) 459(M+1)

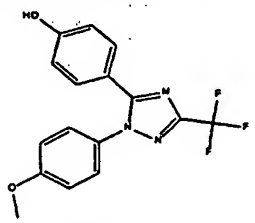
Preparation 32



(P0032)

P0032 was obtained according to a similar manner to that of P0030.
1H NMR (CDCl3, ppm) d 3.85(3H, s), 4.74(2H, q, J=8.3 Hz), 5.06(2H, s), 6.85-7.00(4H, m), 7.21-7.54(9H, m),
MS (ESI, m/e) 456(M+1)

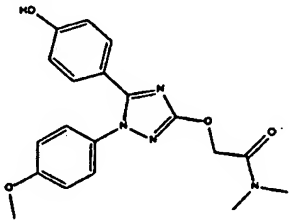
Preparation 33



(P0033)

10% Pd/C(50% wet, 423 mg) and P0050(1.9 g, 4.47 mmol) in 20 ml of methanol were stirred under a hydrogen gas atmosphere at room temperature for 1.5 hours. After filtration, the reaction mixture was evaporated in vacuo to give P0033 (1.39 g, 92.8% yield).
1H NMR (DMSO-d6, ppm) d 3.83(3H, s), 6.70-6.85(2H, m), 7.03-7.18(2H, m), 7.25-7.39(2H, m), 7.40-7.55(2H, m), 10.12(1H, bs),
MS (ESI, m/e) 358(M+Na)

Preparation 34



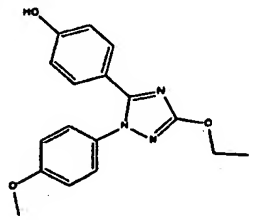
(P0034)

P0034 was obtained according to a similar manner to that of P0033.

1H NMR (DMSO-d6, ppm) d 2.84(3H, s), 2.96(3H, s), 3.80(3H, s), 4.99(2H, s), 6.74(2H, d, J=8.7 Hz), 7.02(2H, d, J=8.9 Hz), 7.17-7.38(4H, m), 9.97(1H, bs),

MS (ESI, m/e) 369(M+1)

Preparation 35



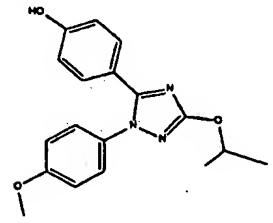
(P0035)

P0035 was obtained according to a similar manner to that of P0033.

1H NMR (DMSO-d6, ppm) d 1.35(3H, t, J=7.0 Hz), 3.80(3H, s), 4.28(2H, q, J=7.0 Hz), 6.64-6.79(2H, m), 6.95-7.08(2H, m), 7.16-7.34(4H, m), 9.95(1H, bs),

MS (ESI, m/e) 312(M+1)

Preparation 36



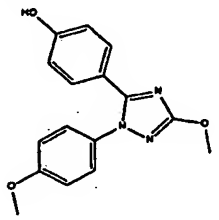
(P0036)

P0036 was obtained according to a similar manner to that of P0033.

1H NMR (CDCl3, ppm) d 1.42(6H, d, J=6.3 Hz), 3.84(3H, s), 5.01(1H, 7th, J=6.1 Hz), 6.62-6.80(3H, m), 6.84-6.98(2H, m), 7.18-7.35(4H, m),

MS (ESI, m/e) 326(M+1)

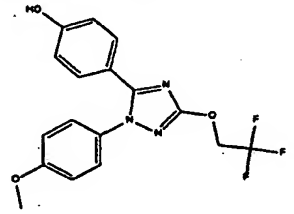
Preparation 37



(P0037)

P0037 was obtained according to a similar manner to that of P0033.
1H NMR (CDCl3, ppm) d 3.84(3H, s), 4.03(3H, s), 6.59-6.74(2H, m), 6.83-6.98(2H, m), 7.16-7.35(4H, m), 8.79(1H, bs),
MS (ESI, m/e) 298(M+1)

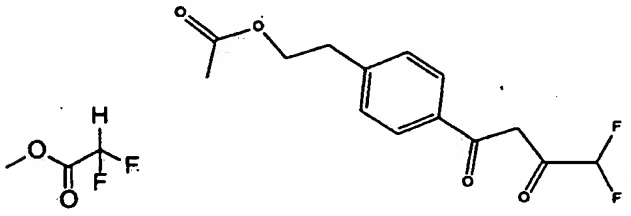
Preparation 38



(P0038)

P0038 was obtained according to a similar manner to that of P0033..
1H NMR (DMSO-d6, ppm) d 3.81(3H, s), 4.98(2H, q, J=8.8 Hz), 6.70-6.83(2H, m), 6.98-7.10(2H, m), 7.18-7.39(4H, m),
MS (ESI, m/e) 366(M+1)

Preparation 39



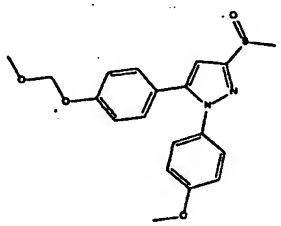
(P0039-0) (P0039)

To a solution of P0001 (20.0g) and P0039-0 (53.4g) in DMF (200ml) was added portionwise NaH (4.27g) under ice-cooling. The reaction mixture was warmed at room temperature and the temperature was kept under 40℃. After stirring for 5 hours, the reaction mixture was poured onto ice-cooled dilHCl and extracted twise

with ethylacetate. The combined organic layer was washed with water (twice) and brine, dried over MgSO4, filtered and evaporated under reduced pressure. The residue was column chromatographed on silica gel (500ml, Hex:EtOAc) to give 12.12g of P0039 as crystal.

mp: 52.6-53.6℃

Preparation 40



(P0040)

To a solution of 4-hydroxybenzophenone (4.16g) and chloromethyl methyl ether (2.46g) in N,N-dimethylacetoamide (15ml) was added portionwise sodium hydride (suspension in mineral oil (60%), 1.22g) over 15 minutes at 0 ℃ . The mixture was stirred for 30 minutes at ambient temperature.

To the reaction mixture was added 2-propanole (0.5ml) , carbon disulfide (2.56g) and portionwise sodium hydride (suspension in mineral oil(60%), 2.50g) over 15 minutes at 25℃. The mixture was stirred at ambient temperature for 1.5 hours, diluted with toluene (20ml) and poured into a mixture of ice and concentrated hydrogen chloride (8 ml) (aqueous layer total 68ml). The resultant mixture was extracted with ethyl acetate , washed with brine, dried over magnesium sulfate, and evaporated.

To the mixture of the resultant residue and sodium hydrogen carbonate (13g) in ethyl acetate (30ml) and water (20ml) was added portionwise the solution of iodine (3.88g) and sodium iodide (8.0g) in water at 0℃. To the mixture was added portionwise 4-Methoxyphenylhydrazine hydrochloride (3.80g) at 0℃ under nitrogen. The mixture was stirred at ambient temperature for 3 hours and the organic layer was seperated, washed with water and brine, dried over magnesium sulfate, and evaporated.

To the solution of the residue in ethyl acetate (30ml) was added

methyl iodide (4.0ml) and triethylamine (10ml) at 0℃. The mixture was stirred for 30 minutes at ambient temperature, washed with water and aqueous potassium carbonate, dried over magnesium sulfate, and evaporated. The residue was column chromatographed on silica gel (80g) ,eluting with a mixture of etyl acetate and toluene (1:20) to give 7.56g of 5-[4-(methoxymethoxy)phenyl]-1-(4-methoxyphenyl)-3-(methylthio)-1H-pyrazole.

To the solution of methyl sulfide (7.56g) in dichloromethane (30 ml) was added a solution of m-chloroperbenzoic acid (80%,4.4g) in dichloromethane (15ml) at 0℃, and the mixture was stirred at 0℃ for 1 hour. The mixture was washed with aqueous potassium carbonate , dried over magnesium sulfate, and evaporated. The residue was column chromatographed on silica gel (80g) ,eluting with ethyl acetate to give 5.43g of 5-[4-(methoxymethoxy)phenyl]-1-(4-methoxyphenyl)-3-(methylsulfinyl)-1H-pyrazole (P0040).

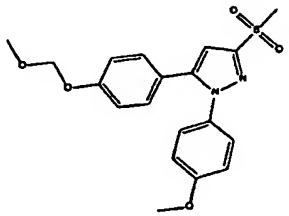
mp.136.9-137.3℃

Mass;373(M+1)

IR(KBr);1054cm-1

NMR(CDCl3, δ) ; 3.00(H, s), 3.48(H, s), 3.83(H, s), 5.17(H, s), 6.88(H, d, J=9.0 Hz), 6.92(H, s), 6.97(H, d, J=8.8 Hz), 7.14(H, d, J=8.8 Hz), 7.22(H, d, J=9.0 Hz),

Preparation 41



(P0041)

To the solution of 5-[4-(methoxymethoxy)phenyl]-1-(4-methoxyphenyl)-3-(methylsulfinyl)-1H-pyrazole (7.56g) in dichloromethane (20 ml) was added m-chloroperbenzoic acid (60%,3.76g) at 0℃, and

the mixture was stirred at 0℃ for 3 hour. The mixture was washed with aqueous sodium hydrogen carbonate , dried over magnesium sulfate, and evaporated. The residue was purified by recrystallization with toluene to give 5.07g of 5-[4-(methoxymethoxy)phenyl]-1-(4-methoxyphenyl)-3-(methylsulfonyl)-1H-pyrazole(P0041).

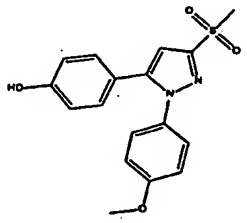
mp.128.0-128.1℃

Mass;389(M+1)

IR(KBr);1300cm-1

NMR(CDCl3, δ) ; 3.29(3H, s), 3.48(3H, s), 3.83(3H, s), 5.17(2H, s), 6.88(2H, d, J=9.0 Hz), 6.93(1H, s), 6.98(2H, d, J=8.8 Hz), 7.13(2H, d, J=8.8 Hz), 7.24(2H, d, J=9.0 Hz),

Preparation 42



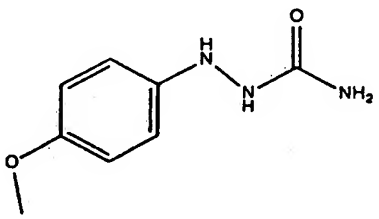
(P0042)

To the solution of 5-[4-(methoxymethoxy)phenyl]-1-(4-methoxyphenyl)-3-(methylsulfonyl)-1H-pyrazole (0.93g) in a mixture of tetrahydrofuran (10ml) and isopropyl alcohole (5ml) was added hydrogen chloride aqueous solution (20%,8ml) at ambient temperature. The solution was stirred for 3 houres,extracted with ethyl acetate , washed with brine,dried over magnesium sulfate,and evaporated to give 0.82g of 4-[1-(4-methoxyphenyl)-3-(methylsulfonyl)-1H-pyrazol-5-yl]phenol (P0042).

Mass;345(M+1)

NMR(DMSO-d6,δ);3.32(3H, s), 3.79(3H, s), 6.73(2H, d, J=8.6 Hz), 7.01(2H, d, J=8.9 Hz), 7.05(1H, s), 7.08(2H, d, J=8.6 Hz), 7.27(2H, d, J=8.9 Hz), 9.84(1H, s),

Preparation 43



(P0043)

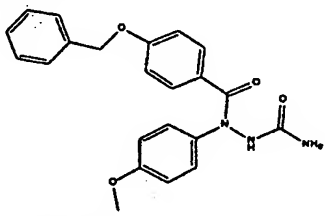
P0043 was obtained according to a similar manner to that of P0079.

1H NMR (DMSO-d6, ppm) d 3.65(3H, s), 5.91(2H, bs), 6.59-6.72(2H, m), 6.72-6.85(2H, m), 7.26(1H, bs), 7.65(1H, bs),
MS (ESI, m/e) 204(M+Na)

Preparation 44

Deleted.

Preparation 45



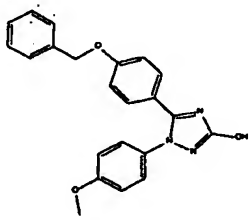
(P0045)

P0045 was obtained according to a similar manner to that of P0080.
MS (ESI, m/e) 414(M+Na)

Preparation 46

Deleted.

Preparation 47



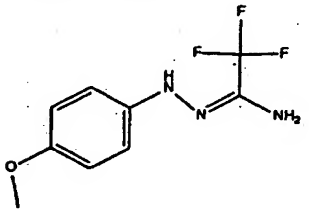
(P0047)

P0047 was obtained according to a similar manner to that of P0081 (20.6 g, 80% yield).

1H NMR (CDCl3, ppm) d 3.83(3H, s), 5.05(2H, s), 6.80-7.05(4H,

m), 7.18-7.55(10H, m),
MS (ESI, m/e) 374(M+1)

Preparation 48



(P0048)

P0048 was obtained according to a similar manner to that of P0082 (3.47 g, 111.1 % yield).
MS (ESI, m/e) 234(M+1)

Preparation 49

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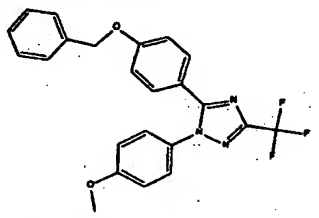
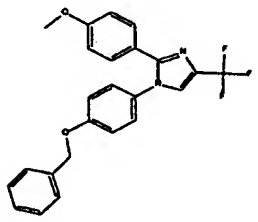
Preparation 50



(P0050)

P0050 was obtained according to a similar manner to that of P0083 (1.93 g, 52.9 % yield).
1H NMR (CDCl3, ppm) d 3.86(3H, s), 5.07(2H, s), 6.85-7.05(4H, m), 7.20-7.58(9H, m),
MS (ESI, m/e) 426(M+1)

Preparation 51



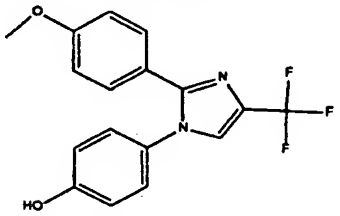
(P0051)

A mixture of
N-(4-benzyloxyphenyl)-4-methoxybenzenecarboximidamide (1 g),

3-bromo-1,1,1-trifluoropropanpone (0.47 ml) and NaHCO3 (506 mg) in IPA (10 ml) was stirred at reflux condition for overnight. After cooling to room temperature, the reaction mixture was filtrated and evaporated in vacuo. Then the residue was poured into water and extracted with ethyl acetate, dried over MgSO4 and evaporated in vacuo. The residue was purified by column chromatography silica-gel eluting with (n-Hexane:AcOEt=1:1) to give 1-(4-benzyloxyphenyl)-4-trifluoromethyl-2-(4-methoxyphenyl)-1H-imidazole (P0051) (0.55 g) as an oil.

NMR (DMSO-d6) d; 3.75 (3H, s), 5.16 (2H, s), 6.86-6.92 (2H, m), 7.09-7.13 (2H, m), 7.25-7.50 (9H, m), 8.08 (1H, d, J=1.4Hz).
IR (Neat): 3120, 3068, 2973, 2843, 1610 cm-1.
Mass m/e : 425 (M++1).

Preparation 52

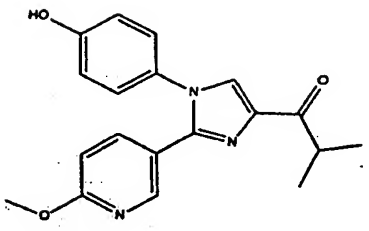


(P0052)

1-(4-benzyloxyphenyl)-4-trifluoromethyl-2-(4-methoxyphenyl)-1H-imidazole (0.55 g) and dry 20% Pd(OH)2/C (200 mg) in EtOH (10 ml) and cyclohexene (5 ml) was stirred at reflux condition for 2 hour and cooled to room temperature. After filtration, the reaction mixture was evaporated in vacuo to give 4-[2-(4-methoxyphenyl)-4-trifluoromethyl-1H-imidazol-1-yl]phenol (0.44 g) (P0052).

m.p. 215-216℃
NMR (DMSO-d6) d; 3.74 (3H, s), 6.81-6.92 (4H, m), 7.16-7.30 (4H, m), 8.03 (1H, d, J=1.3Hz).
IR (KBr): 3149, 3103, 3037, 2964, 2910, 2829, 2690, 2611, 1649, 1614 cm-1.
Mass m/e : 335 (M++1).

Preparation 53



(P0053)

P0053 was obtained in the similar manner that of P0052.

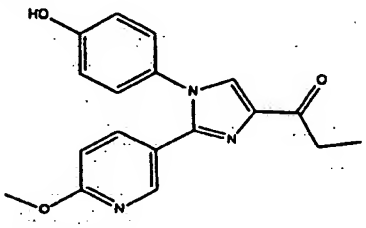
m.p. 185-187℃

NMR (DMSO-d6) d; 1.14 (6H,d, J=6.8Hz), 3.56-3.69 (1H, m), 3.84 (3H, s), 6.79-6.86 (3H, m), 7.17-7.25 (2H, m), 7.67 (1H, dd, J=8.8Hz, 2.4Hz), 8.07 (1H, d, J=2.4Hz), 8.14 (1H, s), 9.98(1H, s).

IR (KBr): 3134, 2972, 2891, 2812, 2744, 2681, 2607, 1676, 1612 cm-1.

Mass m/e : 338 (M++1).

Preparation 54



(P0054)

P0054 was obtained in the similar manner that of P0052.

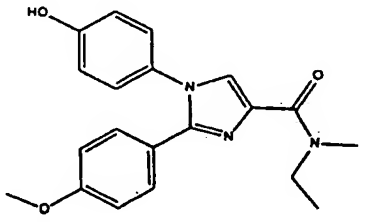
m.p. 221-223℃

NMR (DMSO-d6) d; 1.10 (3H, t, J=7.3Hz), 2.95 (2H, q, J=7.3Hz), 3.84 (3H, s), 6.79-6.88 (3H, m), 7.20 (2H, dt, J=9.6 Hz, 2.7Hz), 7.66 (1H, dd, J=8.7Hz, 2.4Hz), 8.07 (1H, d, J=2.4Hz), 9.97 (1H, s).

IR (KBr): 3215, 3136, 3053, 2978, 2947, 2900, 1676, 1603 cm-1.

Mass m/e : 324 (M++1).

Preparation 55



(P0055)

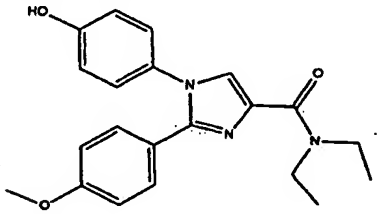
P0055 was obtained in the similar manner that of P0052.

NMR (DMSO-d6) d; 1.10-1.28 (3H, m), 2.90-3.02 (2H, m), 3.40-3.50 (2H, m), 3.74 (3H, s), 3.91-4.03 (1H, m), 6.82 (2H, d, J=8.7Hz), 6.88 (2H, d, J=8.9Hz), 7.11 (1H, s), 7.14 (2H, d, J=8.7Hz), 7.27 (2H, d, J=8.7Hz), 7.67 (1H, s).

IR (KBr): 3126, 3091, 3018, 2968, 2933, 2831, 2738, 2677, 2600, 2476, 1612 cm-1.

Mass m/e : 352 (M++1).

Preparation 56



(P0056)

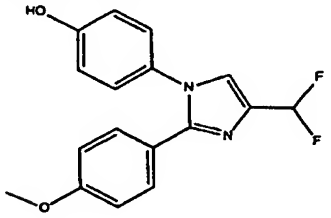
P0056 was obtained in the similar manner that of P0052.

NMR (DMSO-d6) d; 1.02-1.30 (6H, m), 3.22-3.48 (2H, m), 3.73 (3H, s), 3.83-4.02 (2H, m), 6.81-6.92 (4H, m), 7.14 (2H, dd, J=6.7Hz, 2.0Hz), 7.27 (2H, dt, J=9.4Hz, 2.5Hz), 7.66 (1H, s).

IR (KBr): 3145, 3030, 2970, 2937, 2833, 1693, 1606 cm-1.

Mass m/e : 366 (M++1).

Preparation 57



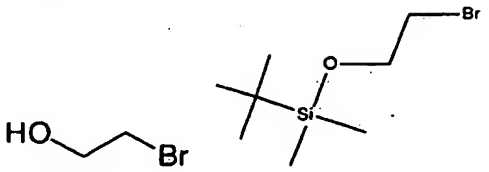
(P0057)

P0057 was obtained according to a similar manner to that of P0052.

1H NMR (DMSO-d6, ppm) d 3.74(3H, s), 6.83(1H, bd, J=55 Hz),

6.75-6.92(4H, m), 7.14(2H, dd, J=2.0,6.7 Hz), 7.27(2H, dd, J=2.0,6.8 Hz), 7.68(1H, t, J=2.2 Hz), 9.90(1H, bs),
MS (ESI, m/e) 317(M+1)

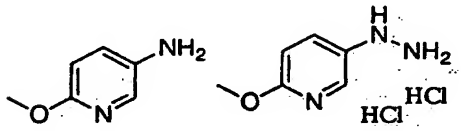
Preparation 58



(P0058-0) (P0058)

To a solution of P0058-0 (5.0g) and imidazole (3.3g) in DMF (40ml) was added portionwise TBDMSCl (6.69g) at room temperature. After stirring overnight, water and hexane was added. The aqueous layer was separated and extracted twice with hexane. The combined organic layer was washed with water (twice) and brine, dried over MgSO4, filtered and evaporated under reduced pressure to give 9.49g (98.3%) of P0058.
IR (film): 2952.5, 2935.1, 1467.6, 1255.4, 1124.3, 1097.3, 838.9, 777.2 cm-1.

Preparation 59

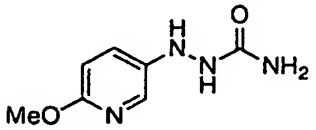


(P0059-0) (P0059)

To the solution of P0059-0 (63.4 g,511 mmol) in 500 ml of conc.HCl at -10℃ under N2, added NaNO2 (37 g, 536 mmol) in 100 ml of water dropwise (about 15min. required), kept the temperature between -10 to 15℃ for 15 more min. Then added Tin(II) chloride dihydrate (288 g, 1.28 mol) in 150 ml of conc.HCl dropwise between -10 to -15℃ (about 30 min. required). After added 100 ml of conc.HCl and 100 ml of water, stirred 1 hour at -10℃ and collected by filtration, washed with Et2O (500 ml at 3 times). Then precipitate was slurried in 500 ml of Et2O, washed with 500 ml of methanol and 500 ml of Et2O, and air dried. (43.7 g, 40% yield).

1H NMR (DMSO-d6, ppm) d 3.82(3H, s), 6.84(1H, d, J=9.0 Hz), 7.57(1H, dd, J=9.0,2.9 Hz), 7.98(1H, d, J=2.9 Hz), 7.87-8.15(1H, m), 10.3(2H, bs),

Preparation 60



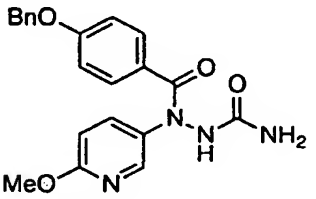
(P0060)

P0060 was obtained according to a similar manner to that of P0079.

1H NMR (DMSO-d6, ppm) d 3.75(3H, s), 5.99(2H, bs), 6.68(1H, d, J=8.8 Hz), 7.12(1H, dd, J=8.8,2.9 Hz), 7.41(1H, bs), 7.60(1H, d, J=2.8 Hz), 7.77(1H, s),

MS (ESI, m/e) 205(M+Na)

Preparation 61



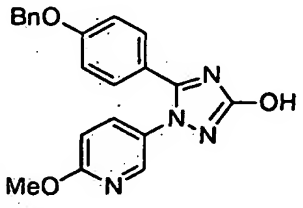
(P0061)

To a suspension of P0060 (200 mg, 1.1mmol) and pyridine (0.1 ml, 1.32 mmol) in 2 ml of dichloromethane and then 4-benzyloxybenzoylchloroide (325 mg, 1.32 mmol) was added under ice bath cooling. The mixture was stirred at room temperature for 2.5 hours and added 40 ml of water. After vigorous shaking, an insoluble material was isolated by filtration, washed with water and toluene and dried in vacuo (330 mg, 76.6% yield).

1H NMR (DMSO-d6, ppm) d 3.83(3H, s), 5.14(2H, s), 6.19(1H, bs), 6.84(1H, bd, J=8.8 Hz), 7.02(2H, bd, J=8.7 Hz), 7.28-7.62(7H, m), 7.65-7.80(1H, m), 8.16(1H, bs), 9.00(1H, bs),

MS (ESI, m/e) 415(M+Na)

Preparation 62



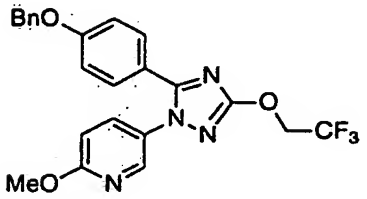
(P0062)

A mixture of P0061 (300 mg, 0.766 mmol) in 1 ml of ethanol and sodium hydroxide (46 mg, 1.15 mmol) in 1ml of water was stirred at 80 °C for 1 hour. After cooling, 1N-HCl was added to the solution and the mixture was adjusted pH to ca. 4. A generated precipitate was isolated by filtration, washed with water and ethyl acetate, dried in vacuo (240 mg, 84% yield).

1H NMR (DMSO-d6, ppm) d 3.89(3H, s), 5.16(2H, s), 6.93(1H, d, J=8.9 Hz), 7.04(2H, d, J=8.8 Hz), 7.29-7.55(8H, m), 7.75(1H, dd, J=8.8,2.6 Hz), 8.19(1H, d, J=2.6 Hz),

MS (ESI, m/e) 375(M+1)

Preparation 63



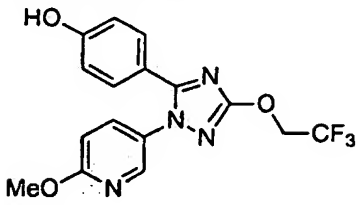
(P0063)

P0063 was obtained according to a similar manner to that of P0030.

1H NMR (CDCl3, ppm) d 3.85(3H, s), 4.74(2H, q, J=8.3 Hz), 5.06(2H, s), 6.85-7.00(4H, m), 7.21-7.54(9H, m),

MS (ESI, m/e) 456(M+1)

Preparation 64



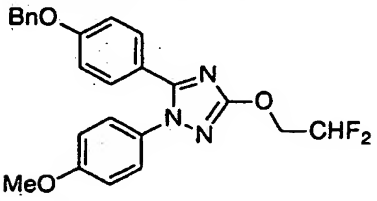
(P0064)

10% Pd/C (50% wet, 500 mg) and P0063 (2.3 g, 5.04 mmol) in 20 ml of methanol were stirred under a hydrogen gas atmosphere at room temperature for 3.5 hours. After filtration through a selite pad, the reaction mixture was evaporated in vacuo to give P0064 (2.0 g, 108.4% yield).

1H NMR (DMSO-d6, ppm) d 3.90(3H, s), 5.00(2H, q, J=8.9 Hz), 6.71-6.82(2H, m), 6.96(1H, d, J=9.1 Hz), 7.22-7.37(2H, m), 7.80(1H, dd, J=8.8,2.8 Hz), 8.23(1H, d, J=2.4 Hz),

MS (ESI, m/e) 367(M+1)

Preparation 65



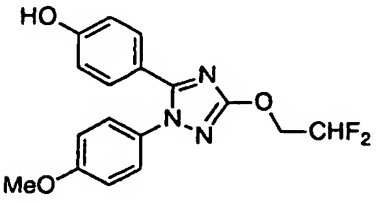
(P0065)

P0065 was obtained according to a similar manner to that of P0030 (2.1 g, 89% yield).

1H NMR (CDCl3, ppm) d 3.85(3H, s), 4.54(2H, dt, J=13.1,4.4 Hz), 5.06(2H, s), 6.17(1H, tt, J=55.3,4.4 Hz), 6.83-6.98(3H, m), 7.21-7.49(10H, m),

MS (ESI, m/e) 438(M+1)

Preparation 66



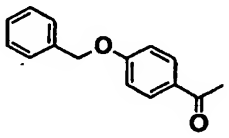
(P0066)

P0066 was obtained according to a similar manner to that of P0033 (1.5 g, 94.5% yield).

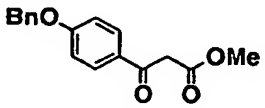
1H NMR (CDCl3, ppm) d 3.85(3H, s), 4.53(2H, dt, J=13.0,4.0 Hz), 6.17(1H, tt, J=55.2,4.5 Hz), 6.15(1H, s), 6.67-6.80(2H, m), 6.86-7.00(2H, m), 7.18-7.40(4H, m),

MS (ESI, m/e) 348(M+1)

Preparation 67



(P0067-0)



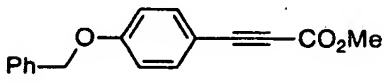
(P0067)

To a solution of P0067-0 (10g) and dimethylcarbonate 5.97g in DMF was added sodium methoxide 4.77g. The mixture was stirred at ambient temperature for 2hours. The mixture was poured into water with 8 ml of conc. HCl, and extracted with AcOEt. The organic layer was dried over magnesium sulfate, and concentrated in vacuo. The residue was purified by silica gel column chromatography to give orange solid. Which was recrystallized from MeOH to give P0067 as white crystals.

NMR (200MHz, CDCl3) 3.75(3H, s), 3.96(2H, s), 5.14(2H, s), 7.02(2H, d, J=8.9 Hz), 7.34-7.45(5H, m), 7.93(2H, d, J=8.9 Hz)

Mass ESI 285(M+H)+ (file platform 7366-1)

Preparation 68



(P0068)

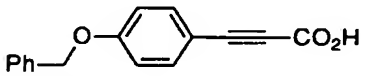
To a solution of triphenylphosphin oxide 294mg in 1,2-dichloroethane 3ml was added trifluoromethanesulfonic anhydride 198mg dropwise under cooling in an ice bath. The mixture was stirred at same temperature for 15minutes, when white precipitates were came out. To this mixture was added P0067 (300mg) in 1,2-dichloroethane 2ml dropwise, followed by addition of Et3N

214mg. The mixture was refluxed for 2hours. The mixture was allowed to cool to ambient temperature and was washed with H2O, sat.aq NaCl, dried over MgSO4, concentrated in vacuo. The residue was purified by silica gel column chromatography eluted with AcOEt / n-hexane = 5%, and 10%. The residue was crystallized from IPE to give P0068 (166mg) as a white powder.

Mass (ESI+) : 289 (M+Na)+

200MHz 1H NMR (DMSO-d6, d) : 3.76(3H, s), 5.18(2H, s), 7.11(2H, d, J=8.8 Hz), 7.33-7.48(5H, m), 7.62(2H, d, J=8.8 Hz)

Preparation 69



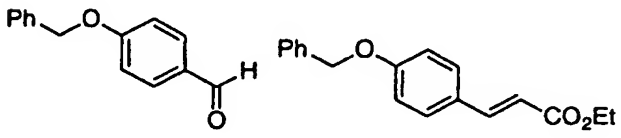
(P0069)

Solid KOH 124mg was dissolved in EtOH 5ml at 50℃. To this solution was added P0068 (196mg). After stirring at same temperature for 2hours, the reaction mixture was allowed to cool to ambient temperature. The mixture was partitioned between 1M HCl and CHCl3. The aqueous layer was reextracted with CHCl3. The combined organic layers were dried over MgSO4, evaporated in vacuo. The residual crystals were collected and washed with IPE to give 1st crop of P0069 (87mg) as a white powder. The mother liqour was concentrated in vacuo and the residual crystals were collected and washed with n-hexane to give 2nd crop of P0069 (39mg) as a slightly reddish powder.

Mass (ESI-) : 251 (M-H)+

200MHz 1H NMR (CDCl3, d) : 5.10(3H, s), 6.97(2H, d, J=8.9 Hz), 7.34-7.43(5H, m), 7.56(2H, d, J=8.9 Hz)

Preparation 70

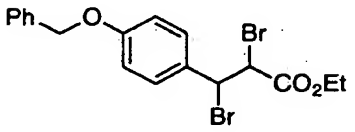


(P0070-0) (P0070)

To a solution of P0070-0 (2g) and triethylphosphonoacetate 2.32g in DMF 20ml was added 60% NaH 490mg in two portions with cooling on ice bath. The mixture was stirred at same temperature for 1hour, and then poured into ice water containing NH4Cl. The mixture was stirred for a while, and white precipitates were collected and washed with water and 10% aqueous IPA to give P0070.

200MHz 1H NMR (CDCl3, d) : 1.33(3H, t, J=7.2 Hz), 4.25(2H, q, J=7.2 Hz), 5.10(2H, s), 6.31(1H, d, J=16.0 Hz), 6.97(2H, d, J=8.7 Hz), 7.32-7.50(7H, m), 7.64(1H, d, J=16.0 Hz)

Preparation 71

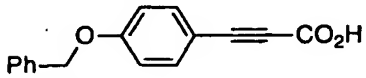


(P0071)

To a solution of P0070 (2.79g) in CH2Cl2 28ml was added bromine 1.66g dropwise under ice bath cooling. The mixture was stirred at same temperature for 30minutes. The reaction mixture was poured into 5% aqueous solution of Na2S2O3, and partitioned. The organic layer was washed with sat.aqNaHCO3, sat.aqNaCl, dried over MgSO4, concentrated in vacuo. The residual crystals were collected and washed with n-hexane to give P0071 (3.07g) as a pale yellow powder.

200MHz 1H NMR (CDCl3, d) : 1.38(3H, t, J=7.2 Hz), 4.35(2H, q, J=7.2 Hz), 4.81(1H, d, J=11.8 Hz), 5.07(2H, s), 5.35(1H, d, J=11.8 Hz), 6.98(2H, d, J=8.7 Hz), 7.34(2H, d, J=8.7 Hz), 7.32-7.45(5H, m)

Preparation 72



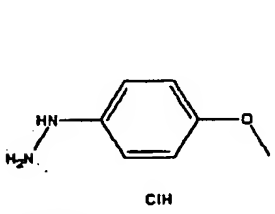
(P0072)

85% solid KOH 1.73g was dissolved in 95% aqueous EtOH 20ml at 50℃. P0071 (3.05g) was added in one portion and the mixture was

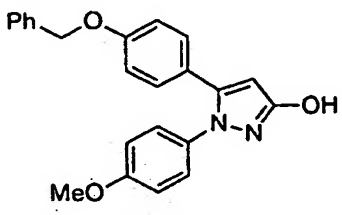
refluxed for 9hours. To this mixture was added a solution of 85% KOH 0.32g dissolved in 95% aqueous EtOH 10ml and refluxed for 5hours. The mixture was cooled in an ice bath, precipitates were collected and washed with EtOH. The crystals were suspended in AcOEt and H2O, cooled in an ice bath, acidified by 3M HCl and 1M HCl. The mixture was partitioned and the organic layer was washed with H2O, dried over MgSO4, concentrated in vacuo. The residual solid was collected and washed with IPE-n-hexane to give P0072 (0.67g) as a white powder.

200MHz 1H NMR (CDCl3, d) : 5.10(3H, s), 6.97(2H, d, J=8.9 Hz), 7.34-7.43(5H, m), 7.56(2H, d, J=8.9 Hz)

Preparation 73



(P0073-0)



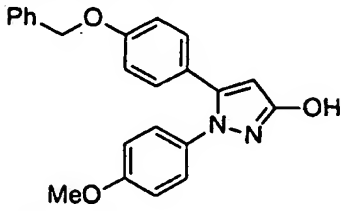
(P0073)

To a solution of P0072(99.9mg) and HOBT 64.2mg in N-methylpyrrolidone 1ml was added WSCD·HCl 91.1mg and the mixture was stirred at ambient temperature for 20minutes. In another flask, diisopropylethylamine 76.8mg was added to a suspension of P0073-0 (83.0mg) in N-methylpyrrolidone 1ml and stirred at ambient temperature until all P0073-0 was dissolved. The solution of P0073-0 was added to the reaction flask and the mixture was stirred at ambient temperature for 1hour. The mixture was partitioned between AcOEt and H2O, washed with sat.aqNaHCO3, sat.aqNaCl, dried over MgSO4, and concentrated in vacuo.The residue was dissolved in CH2Cl2 3ml, and stirred at ambient temperature for 24hours. The mixture was concentrated in vacuo. The residual crystals were suspended in hot AcOEt, cooled with stirring, collected and washed with AcOEt to give P0073 (90.9mg) as a white powder.

Mass (ESI+) : 373 (M+H)+

200MHz 1H NMR (DMSO-d6, d) : 3.75(3H, s), 5.08(2H, s), 5.81(1H, s), 6.90(2H, d, J=9.0 Hz), 6.96(2H, d, J=9.0 Hz), 7.10(2H, d, J=9.0 Hz), 7.12(2H, d, J=9.0 Hz), 7.32-7.47(5H, m), 10.00(1H, s)

Preparation 74

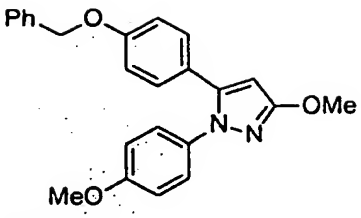


(P0074)

To a solution of P0072 (670mg) and HOBT 431mg in N-methylpyrrolidone 6ml was added WSCD·HCl 611mg and the mixture was stirred at ambient temperature for 10minutes. In another flask, diisopropylethylamine 824mg was added to a suspension of P0073-0 (557mg) in N-methylpyrrolidone 4ml and stirred at ambient temperature until all P0073-0 was dissolved. The solution of P0073-0 was added to the reaction flask and the mixture was stirred at ambient temperature for 2hours. The mixture was partitioned between AcOEt and 0.1M HClaq and the aqueous layer was reextracted with AcOEt. The combined organic layers were washed with sat.aqNaHCO3, sat.aqNaCl, dried over MgSO4, and concentrated in vacuo. The residue was dissolved in CH2Cl2 15ml and Pd(PPh3)4 30.7mg was added. After stirring at ambient temperature overnight, precipitates were collected and washed with CH2Cl2 and AcOEt to give P0074 (633mg) as a pale yellow powder.

200MHz 1H NMR (DMSO-d6, d) : 3.75(3H, s), 5.08(2H, s), 5.81(1H, s), 6.90(2H, d, J=9.0 Hz), 6.96(2H, d, J=9.0 Hz), 7.10(2H, d, J=9.0 Hz), 7.12(2H, d, J=9.0 Hz), 7.32-7.47(5H, m), 10.00(1H, s)

Preparation 75



(P0075)

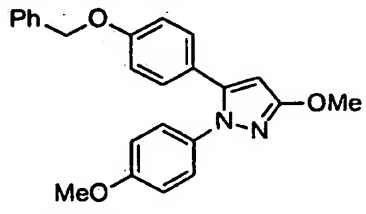
To a suspension of P0074 (20.9mg) and K2CO3 23.3mg in DMSO 0.5ml was added dimethylsulfate 10.6mg and the mixture was stirred at ambient temperature for 1hour. The mixture was partitioned between AcOEt and H2O, and the organic layer was washed with sat.aqNaCl, dried over MgSO4, concentrated in vacuo. The residue was purified by preparative thin layer chromatography developed with AcOEt / n-hexane = 25%. The obtained crystals were crystallized from IPE to give P0075 (12.0mg) as white crystals.

Mass (ESI+) : 387 (M+H)+

200MHz 1H NMR (DMSO-d6, d) : 3.76(3H, s), 3.83(3H, s), 5.08(2H, s), 6.04(1H, s), 6.92(2H, d, J=9.0 Hz), 6.97(2H, d, J=9.0 Hz), 7.11-7.17(4H, m), 7.30-7.50(5H, m)

200MHz 1H NMR (CDCl3, d) : 3.80(3H, s), 3.97(3H, s), 5.04(2H, s), 5.88(1H, s), 6.82(2H, d, J=9.0 Hz), 6.88(2H, d, J=8.9 Hz), 7.11-7.21(4H, m), 7.34-7.43(5H, m)

Preparation 76



(P0076)

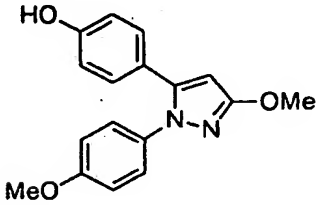
To suspension of P0074 (818mg) and K2CO3 911mg in DMF 6ml was added dimethylcarbonate 0.56ml. The mixture was stirred at 120℃ for 2hours. Additional dimethylcarbonate 1ml was added and stirred at 120℃ for 8hours. The mixture was partitioned between AcOEt and H2O, and the aq layer was reextracted with AcOEt. The combined organic layers were washed with sat.aqNaCl, dried over MgSO4, concentrated in vacuo. The residue was purified by silica gel

column chromatography eluted with AcOEt / n-hexane = 30%. The residue was crystallized from AcOEt 2.5ml and n-hexane 5ml to give P0076 (583mg) as white crystals.

200MHz 1H NMR (DMSO-d6, d) : 3.76(3H, s), 3.83(3H, s), 5.08(2H, s), 6.04(1H, s), 6.92(2H, d, J=9.0 Hz), 6.97(2H, d, J=9.0 Hz), 7.11-7.17(4H, m), 7.30-7.50(5H, m)

200MHz 1H NMR (CDCl3, d) : 3.80(3H, s), 3.97(3H, s), 5.04(2H, s), 5.88(1H, s), 6.82(2H, d, J=9.0 Hz), 6.88(2H, d, J=8.9 Hz), 7.11-7.21(4H, m), 7.34-7.43(5H, m)

Preparation 77



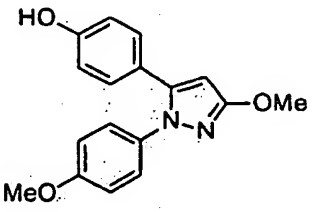
(P0077)

A mixture of 10% Pd-C 50% wet 50mg and P0076 (261mg) in AcOEt 2ml and MeOH 2ml was hydrogenated under H2 1atm at ambient temperature for 1day. The additional 10% Pd-C 50% wet 50mg was added and the mixture was hydrogenated under H2 3.5atm at ambient temperature for 3hours. The catalyst was filtered off and the filtrate and combined washings were concentrated in vacuo. The residue was dissolved in AcOEt, dried over MgSO4, and concentrated in vacuo. The residue was crystallized from AcOEt-n-hexane to give P0077 (146mg) as a white powder.

Mass (ESI+) : 297 (M+H)+

200MHz 1H NMR (DMSO-d6, d) : 3.75(3H, s), 3.83(3H, s), 5.98(1H, s), 6.70(2H, d, J=8.6 Hz), 6.91(2H, d, J=8.9 Hz), 7.01(2H, d, J=8.6 Hz), 7.12(2H, d, J=8.9 Hz), 9.69(1H, s)

Preparation 78



(P0078)

To a solution of ammmonium formate 455mg in H2O 1ml was added EtOH 6ml, P0076 (558mg), THF 1ml, and 10% Pd-C 50% wet 60mg successively. The mixture was refluxed for 1hour. The catalyst was removed by filtration. The filtrate and combined washings were concentrated in vacuo. The residue was partitioned between AcOEt and H2O, and the organic layer was washed with sat.aqNaCl, dried over MgSO4, concentrated in vacuo. The residual crystals were recrystallized from AcOEt 3ml and n-hexane 3ml to give P0078 (335mg) as white crystals.

Mass (ESI+) : 297 (M+H)+

Preparation 79

Under ice-bath cooling, potassium cyanate (1.71 g, 21.1 mmol) was added to a suspension of 4-methoxyphenylhydrazine hydrochloride (3.35 g, 19.2 mmol) in water (40 mL). The mixture was stirred for 1 hour at the same temperature. And then the mixture was warmed to room temperature and stirred for 12 hours. An insoluble material was isolated by filtration, washed with water, and dried in vacuo to give 2-(4-methoxyphenyl)hydrazine-carboxamide (2.45 g, 70.5% yield)(P0079).

1H NMR (DMSO-d6, ppm) δ 7.64(s, 1H), 7.26(s, 1H), 6.78(d, J = 8.8 Hz, 2H), 6.67(d, J = 8.8 Hz, 2H), 5.90(s, 2H), 3.66(s, 3H)
MS (ESI, m/e) 223(M+1+MeCN)

Preparation 80

To a suspension of 2-(4-methoxyphenyl)hydrazinecarboxamide (1.81 g, 9.99 mmol) in 20 mL of toluene, pyridine (1.01 mL, 12.5 mmol) and then a solution of 4-methoxybenzoyl chloride (2.13 g, 12.5 mmol) in 10 mL of toluene were added. The mixture was refluxed

with stirring for 1 hour. After cooling, 500 mL of ethyl acetate - tetrahydrofuran (9:1) and 100 mL of water were added to the mixture. After vigorous shaking, an insoluble material was isolated by filtration and dried in vacuo to give 2-(4-methoxybenzoyl)-2-(4-methoxyphenyl)hydrazinecarboxamide (1.95 g, 61.9% yield)(P0080).

1H NMR (DMSO-d6, ppm) δ 8.86(br s, 1H), 7.49(br d, J = 7.4 Hz, 2H), 7.28(br s, 2H), 6.89(m, 4H), 3.77(s, 3H), 3.73(s, 3H)
MS (ESI, m/e) 316(M+1)

Preparation 81

A mixture of 2-(4-methoxybenzoyl)-2-(4-methoxyphenyl)-hydrazinecarboxamide (1.9 g, 6.03 mmol) in 10% potassium hydroxide solution (16 mL) - ethanol (8 mL) was heated at 60 °C for 1.5 hours. After cooling, the solvent was removed under reduced pressure. Water was added to the residue and the mixture was adjusted pH to ca. 2. A generated precipitate was isolated by filtration, washed with water, and dried in vacuo to give 1,5-bis(4-methoxyphenyl)-1H-1,2,4-triazol-3-ol (1.51 g, 84.3% yield)(P0081).

1H NMR (DMSO-d6, ppm) δ 7.32(d, J = 8.9 Hz, 2H), 7.28(d, J = 8.9 Hz, 2H), 7.01(d, J = 8.9 Hz, 2H), 6.93(d, J = 8.9 Hz, 2H), 3.80(s, 3H), 3.77(s, 3H)
MS (ESI, m/e) 298(M+1)

Preparation 82

To a solution of trifluoroacetoamidine (4.24 g, 37.8 mmol) in methanol (20 mL), were added 4-methoxyphenylhydrazine hydrochloride (4.72 g, 27 mmol) and then triethylamine (3.77 mL, 27 mmol) at room temperature. The mixture was stirred for 6 hours. The solvent was removed under reduced pressure. 20 mL of water and 50 mL of ethyl acetate - tetrahydrofuran (9:1) were added to the residue and the organic layer was separated and the

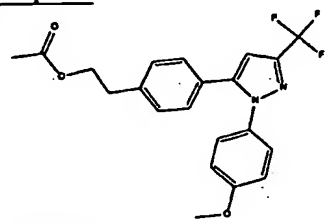
aqueous layer was extracted with 50 mL of ethyl acetate - tetrahydrofuran (9:1). A combined organic layer was washed with water and brine, and dried over magnesium sulfate. The solvent was removed under reduced pressure to give 2,2,2-trifluoro-N'-(4-methoxyphenyl)ethanehydrazonamide (6.82 g, 108.2% yield)(P0082). The residue was used for the next reaction without purification.

Preparation 83

To a solution of 2,2,2-trifluoro-N'-(4-methoxyphenyl)-ethanehydrazonamide (0.92 g, 3.95 mmol) in 10 mL of dioxane, were added pyridine (0.319 mL, 3.95 mmol) and a solution of 4-methoxybenzoyl chloride (673 mg, 3.95 mmol) in 3 mL of dioxane. The mixture was refluxed with stirring for 12 hours. The solvent was removed under reduced pressure. 50 mL of dichloromethane and 20 mL of 0.1 N hydrochloric acid were added to the residue and the organic layer was separated. The aqueous layer was extracted with 50 mL of dichloromethane. A combined organic layer was washed with 0.1 N hydrochloric acid and brine and dried over magnesium sulfate.The solvent was removed under reduced pressure. The residue was purified by silica gel column chromatography (toluene - ethyl acetate 9:1) and then recrystallized with diisopropyl ether - hexane to give pale brown needle of 1,5-bis(4-methoxyphenyl)-3-(trifluoromethyl)-1H-1,2,4-triazole (0.67 g, 48.6% yield)(P0083).

1H NMR (DMSO-d6, ppm) δ 7.45 (t, J = 8.9 Hz, 4H), 7.09(d, J = 8.9 Hz, 2H), 6.98(d, J = 8.9 Hz, 2H), 3.83(s, 3H), 3.78(s, 3H)
MS (ESI, m/e) 350(M+1)

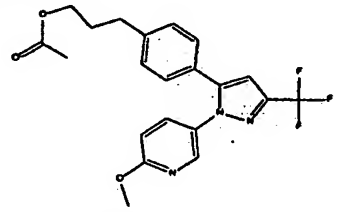
Example 1



(E0001)

A mixture of P0003 (2.9g) and 4-methoxyphenylhydrazine (1.68g) in acetic acid (30ml) was stirred at room temperature for 15 hours. After addition of water, the mixture was extracted twice with toluene. The combined organic layer was washed with water (twice), sat.NaHCO3, water and brine, dried over MgSO4, filtered and evaporated under reduced pressure. The residue was column chromatographed on silica gel (Hex/EtOAc = 8:1-4:1) to give 2.2g (57%) of E0001 as an oil.
IR (film): 1737.6, 1511.9, 1240.0, 1159.0, 1130.1 cm-1.

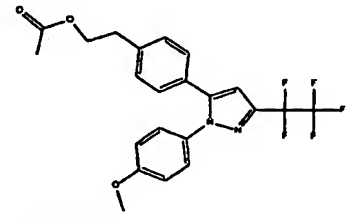
Example 2



(No. E0002)

E0002 was prepared from P0004 in a similar manner to that of E0001.
Mass (ESI+) : 420 (M+H)+
200MHz 1H NMR (DMSO-d6, d) : 1.79-1.94(2H, m), 1.98(3H, s), 2.60-2.68(2H, m), 3.88(3H, s), 3.98(2H, t, J=6.5 Hz), 6.92(1H, d, J=8.9 Hz), 7.18(1H, s), 7.24(4H, s), 7.75(1H, dd, J=2.7,8.9 Hz), 8.48(1H, d, J=2.7 Hz)

Example 3



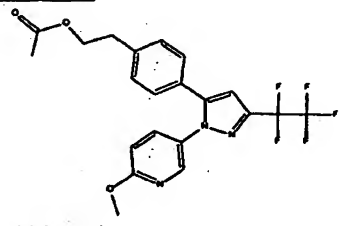
(E0003)

E0003 (175.7mg) was prepared from P0007 (590mg) and 4-methoxyphenylhydrazine hydrochloride (332mg) in a similar manner to that of E0001.

Mass (ESI+) : 455 (M+H)+

200MHz 1H NMR (DMSO-d6, d) : 1.96(3H, s), 2.88(2H, t, J=6.8 Hz), 3.79(3H, s), 4.20(2H, t, J=6.8 Hz), 6.99(2H, d, J=8.9 Hz), 7.15(1H, s), 7.17-7.30(6H, m)

Example 4



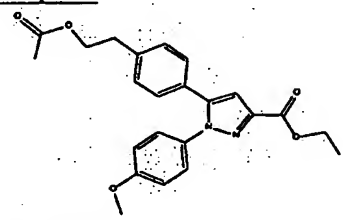
(E0004)

E0004 was prepared from P0007 in a similar manner to that of E0001.

Mass (API-ES positive) : 456 (M+H)+ , 478 (M+Na)+

200MHz 1H NMR (DMSO-d6, d) : 1.96(3H, s), 2.89(2H, t, J=6.8 Hz), 3.88(3H, s), 4.21(2H, t, J=6.8 Hz), 6.92(1H, d, J=8.8 Hz), 7.15-7.35(4H, m), 7.21(1H, s), 7.76(1H, dd, J=2.7,8.8 Hz), 8.17(1H, d, J=2.7 Hz)

Example 5



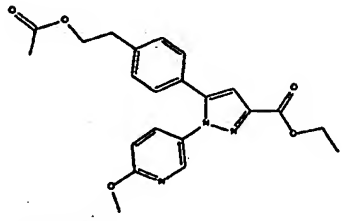
(E0005)

E0005 was prepared in a similar manner to that of E0001.

Mass (ESI+) 409(M+H)+, 431(M+Na)+

NMR: SE20.059 200MHz 1H NMR (DMSO-d6, d) : 1.31(3H, t, J=7.1 Hz), 1.96(3H, s), 2.87(2H, t, J=6.8 Hz), 3.79(3H, s), 4.20(2H, t, J=6.8 Hz), 4.32(2H, q, J=7.1 Hz), 6.99(2H, d, J=9.0 Hz), 7.08(1H, s), 7.16-7.28(6H, m)

Example 6



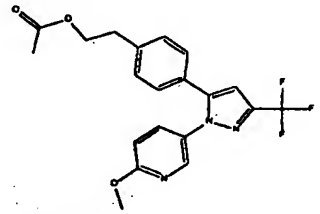
(E0006)

E0006 was prepared in a similar manner to that of E0001.

Mass (ESI+) : 410 (M+H)+

200MHz 1H NMR (DMSO-d6, d) : 1.32(3H, t, J=7.1 Hz), 1.96(3H, s), 2.89(2H, t, J=6.8 Hz), 3.88(3H, s), 4.21(2H, t, J=6.8 Hz), 4.33(2H, q, J=7.1 Hz), 6.92(1H, d, J=8.8 Hz), 7.12(1H, s), 7.19-7.32(4H, m), 7.73(1H, dd, J=2.7,8.8 Hz), 8.14(1H, d, J=2.7 Hz)

Example 7



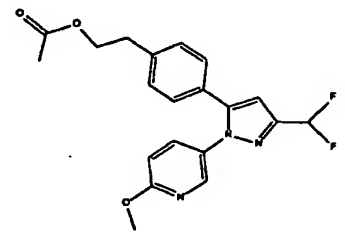
(E0007)

E0007 was prepared in a similar manner to that of E0001.

Mass (API-ES positive) : 406(M+H)+ , 428(M+Na)+

200MHz 1H NMR (DMSO-d6, d) : 1.96(3H, s), 2.89(2H, t, J=6.7 Hz), 3.88(3H, s), 4.21(2H, t, J=6.7 Hz), 6.92(1H, d, J=8.8 Hz), 7.20(1H, s), 7.24(2H, d, J=8.7 Hz), 7.30(2H, d, J=8.7 Hz), 7.76(1H, dd, J=2.7, 8.8 Hz), 8.18(1H, d, J=2.7 Hz)

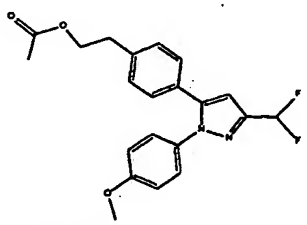
Example 8



(E0008)

E0008 was obtained according to a similar manner to that of E0001.

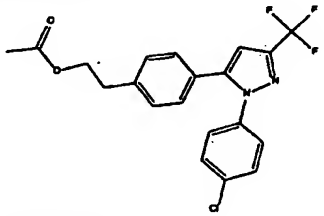
Example 9



(E0009)

E0009 was obtained according to a similar manner to that of E0001.

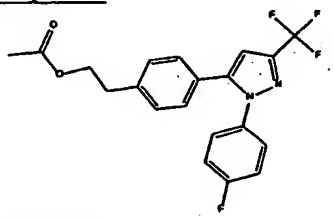
Example 10



(E0010)

E0010 was obtained according to a similar manner to that of E0001.

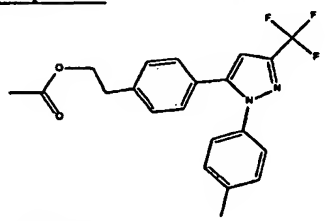
Example 11



(E0011)

E0011 was obtained according to a similar manner to that of E0001.

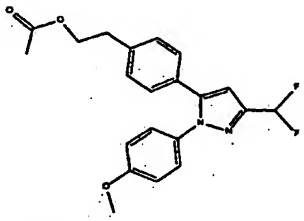
Example 12



(E0012)

E0012 was obtained according to a similar manner to that of E0001.

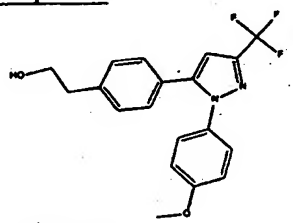
Example 13



(E0013)

E0013 was obtained according to a similar manner to that of E0001.

Example 14



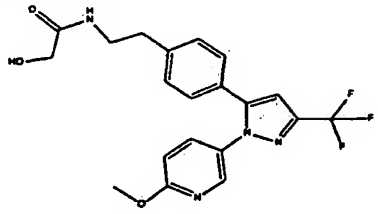
(E0014)

A mixture of E0001 (2.0g) and 1N NaOH (15ml) in THF (40ml) was stirred at room temperature for 5 hours. After the reaction was completed, the mixture was neutralized with 1N HCl (15ml), extracted twice with ethylacetate, washed with 1N HCl, sat.NaHCO3, and brine, dried over NA2SO4, filtered and evaporated under reduced pressure. The residue was column chromatographed on silica gel (H/EA = 2:1-1:1) to give 1.14g (64%) of E0014 as a crystal.

mp: 103-104℃

IR (film): 3396.0, 1513.9, 1467.6, 1238.1, 1160.9, 1132.0 cm-1.

Example 15



(E0015)

E0015 was prepared from E0122 in a similar manner to that of E0014.

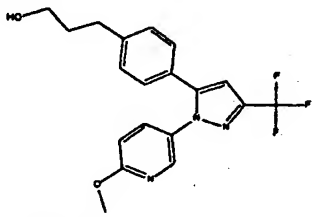
IR (neat) : 3359, 3332, 3325, 1658, 1651, 1624, 1614, 1545, 1533, 1500cm-1

Mass (ESI+) : 421 (M+H)+

200MHz 1H NMR (DMSO-d6, d) : 2.71-2.79(2H, m), 3.28-3.39(2H, m), 3.76(2H, brs), 3.88(3H, s), 5.47(1H, br), 6.92(1H, d, J=8.9 Hz), 7.18(1H, s), 7.24(4H, s), 7.74(1H, dd,

J=2.7, 8.9 Hz), 7.80(1H, t, J=5.9 Hz), 8.19(1H, d, J=2.7 Hz)

Example 16



(E0016)

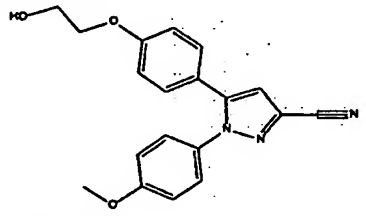
E0016 was prepared from E0002 in a similar manner to that of E0014.

IR (neat) : 3433, 3423, 3398, 3367, 2945, 1612, 1500cm-1

Mass (ESI+) : 378 (M+H)+

200MHz 1H NMR (DMSO-d6, d) : 1.62-1.77(2H, m), 2.57-3.65(2H, m), 3.34-3.44(2H, m), 3.88(3H, s), 4.48(1H, t, J=5.1 Hz), 6.92(1H, d, J=8.9 Hz), 7.17(1H, s), 7.23(4H, s), 7.76(1H, dd, J=8.9,2.8 Hz), 8.18(1H, d, J=2.8 Hz)

Example 17



(E0017)

E0017 was prepared from E0268 in a similar manner to that of E0014.

white powder

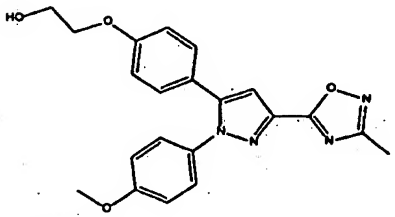
mp. 91-92℃

IR (KBr) : 3491, 3471, 3437, 2941, 2239, 1610, 1508cm-1

Mass (ESI+) : 336 (M+H)+

200MHz 1H NMR (DMSO-d6, d) : 3.65-3.73(2H, m), 3.79(3H, s), 3.95-4.05(2H, m), 4.87(1H, t, J=5.4 Hz), 6.93(2H, d, J=8.8 Hz), 7.00(2H, d, J=9.0 Hz), 7.16(2H, d, J=8.8 Hz), 7.28(2H, d, J=9.0 Hz), 7.32(1H, s)

Example 18



(E0018)

E0018 was prepared from E0264 in a similar manner to that of E0014.

white powder

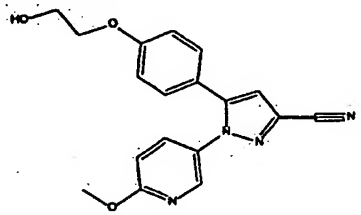
mp. 158-159℃

IR (KBr) : 3399, 2955, 1707, 1693, 1647, 1614, 1566, 1547, 1529, 1512cm-1

Mass (ESI+) : 393 (M+H)+

200MHz 1H NMR (DMSO-d6, d) : 2.44(3H, s), 3.66-3.74(2H, m), 3.80(3H, s), 3.96-4.02(2H, m), 4.88(1H, t, J=5.4 Hz), 6.94(2H, d, J=8.7 Hz), 7.02(2H, d, J=8.9 Hz), 7.22(2H, d, J=8.7 Hz), 7.26(1H, s), 7.31(2H, d, J=8.9 Hz)

Example 19



(E0019)

E0019 was prepared from E0269 in a similar manner to that of E0014.

white powder

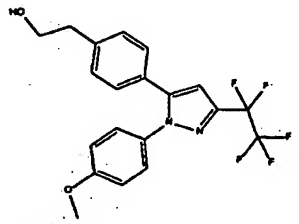
mp. 105-107℃

IR (KBr) : 3529, 3437, 2956, 1610, 1570, 1547, 1529cm-1

Mass (ESI+) : 337 (M+H)+

200MHz 1H NMR (DMSO-d6, d) : 3.65-3.73(2H, m), 3.88(3H, s), 3.96-4.02(2H, m), 4.87(1H, t, J=5.3 Hz), 6.93(1H, d, J=8.8 Hz), 6.96(2H, d, J=8.7 Hz), 7.21(2H, d, J=8.7 Hz), 7.35(1H, s), 7.73(1H, dd, J=2.7,8.8 Hz), 8.20(1H, d, J=2.7 Hz)

Example 20



(E0020)

E0020 was prepared from E0003 in a similar manner to that of E0014.

white powder

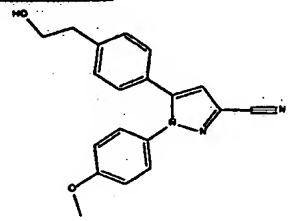
mp. 97-98℃

IR (KBr) : 3427, 2960, 1608, 1516cm-1

Mass (ESI+) : 413 (M+H)+

200MHz 1H NMR (DMSO-d6, d) : 2.71(2H, t, J=6.9 Hz), 3.54-3.65(2H, m), 3.79(3H, s), 4.64(1H, t, J=5.1 Hz), 7.00(2H, d, J=9.0 Hz), 7.12(1H, s), 7.15-7.33(4H, m), 7.29(2H, d, J=9.0 Hz)

Example 21



(No. E0021)

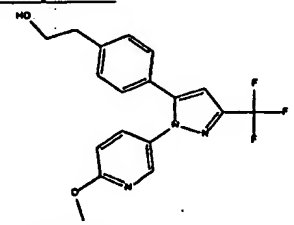
E0021 was prepared in a similar manner to that of E0014.

IR (neat) : 3435, 3425, 3406, 3398, 3367, 1691, 1658, 1647, 1614, 1547, 1512cm-1

Mass (ESI+) : 320 (M+H)+ , 361(M+CH3CN+H)+

200MHz 1H NMR (DMSO-d6, d) : 2.71(2H, t, J=6.8 Hz), 3.54-3.64(2H, m), 3.79(3H, s), 4.64(1H, t, J=5.2 Hz), 7.00(2H, d, J=8.9 Hz), 7.15(2H, d, J=8.3 Hz), 7.23(2H, d, J=8.3 Hz), 7.29(2H, d, J=8.9 Hz), 7.34(1H, s)

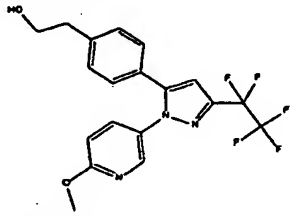
Example 22



(E0022)

E0022 was prepared from E0007 in a similar manner to that of E0014.
white powder
mp. 89-92℃
IR (KBr) : 3481, 2947, 1608, 1496cm-1
Mass (ESI+) : 364 (M+H)+
200MHz 1H NMR (DMSO-d6, d) : 2.72(2H, t, J=6.8 Hz), 3.55-3.65(2H, m), 3.88(3H, s), 4.65(1H, t, J=5.2 Hz), 6.92(1H, d, J=8.8 Hz), 7.16(1H, s), 7.19-7.28(4H, m), 7.77(1H, dd, J=2.6,8.8 Hz), 8.19(1H, d, J=2.6 Hz)

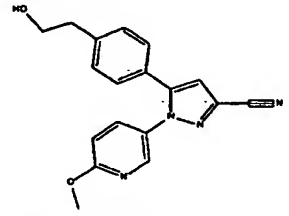
Example 23



(E0023)

E0023 was prepared from E0004 in a similar manner to that of E0014.
IR (neat) : 3400, 2951, 1610, 1502cm-1
Mass (API-ES positive) : 414 (M+H)+ , 436 (M+Na)+
200MHz 1H NMR (DMSO-d6, d) : 2.72(2H, t, J=6.9 Hz), 3.51-3.65(2H, m), 3.88(3H, s), 4.65(1H, t, J=5.1 Hz), 6.93(1H, d, J=8.8 Hz), 7.15-7.35(4H, m), 7.18(1H, s), 7.77(1H, dd, J=2.7,8.8 Hz), 8.18(1H, d, J=2.7 Hz)

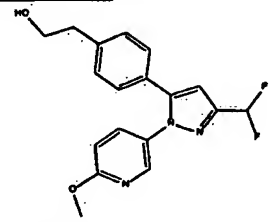
Example 24



(No. E0024)

E0024 104.4mg was prepared in a similar manner to that of E0014.
IR (neat) : 3433, 3423, 3398, 2947, 2873, 2243, 1608cm-1
Mass (ESI+) : 321 (M+H)+
200MHz 1H NMR (DMSO-d6, d) : 2.72(2H, t, J=6.8 Hz), 3.55-3.65(2H, m), 3.88(3H, s), 4.65(1H, t, J=5.1 Hz), 6.93(1H, d, J=8.8 Hz), 7.19(2H, d, J=8.4 Hz), 7.26(2H, d, J=8.4 Hz), 7.38(1H, s), 7.76(1H, dd, J=2.7,8.8 Hz), 8.21(1H, d, J=2.7 Hz)

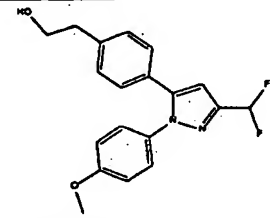
Example 25



(E0025)

E0025 was obtained according to a similar manner to that of E0014.

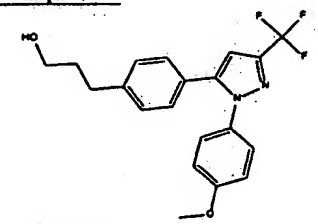
Example 26



(E0026)

E0026 was obtained according to a similar manner to that of E0014.

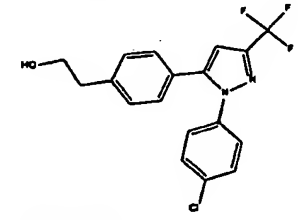
Example 27



(E0027)

E0027 was obtained according to a similar manner to that of E0014.

Example 28

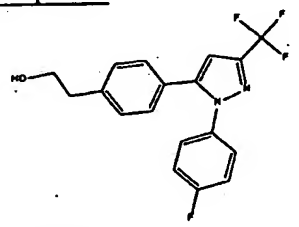


(E0028)

E0028 was obtained according to a similar manner to that of E0014.

IR (film): 3392.2, 1494.6, 1236.2, 1160.9, 1133.9, 1095.4, 975.8, 833.1 cm-1.

Example 29



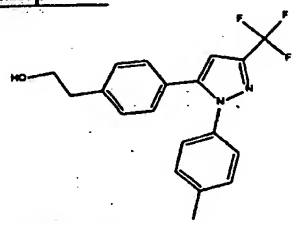
(E0029)

E0029 was obtained according to a similar manner to that of E0014.

IR (film): 3374.8, 1511.9, 1471.4, 1274.7, 1232.3, 1160.9, 1133.9, 977.7, 842.7, 811.9 cm-1.

mp: 82-83 oC

Example 30

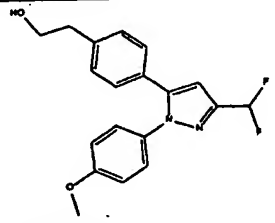


(E0030)

E0030 was obtained according to a similar manner to that of E0014.

IR (film): 3386.4, 1511.9, 1471.4, 1236.2, 1159.0, 1132.0, 1047.2, 975.8, 817.7 cm-1.

Example 31

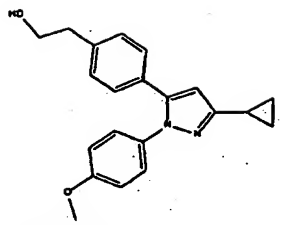


(E0031)

E0031 was obtained according to a similar manner to that of E0014.

IR (film): 3399.9, 1610.3, 1513.9, 1459.9, 1251.6, 1172.5, 1083.8, 1033.7, 836.9, 802.2 cm-1. (FS7081)

Example 32



(E0032)

P0018 (277mg) and 4-methoxyphenylhydrazine hydrochloride (209mg) in EtOH:AcOH=20:1 6ml was refluxed for 2hours. The mixture was partitioned between AcOEt and H2O. The organic layer was washed successively with 1M HCl, saturated aqueous sodium bicarbonate solution, and saturated aqueous sodium chloride solution, dried over magnesium sulfate, and concentrated in vacuo. The residue was purified by silica gel column chromatography eluted with AcOEt / n-hexane = 30%, 40%, 50%. Thepure fraction was collected and concentrated in vacuo. The residue was crystallized from AcOEt / n-hexane to give E0032 (95.6mg) as a white powder.

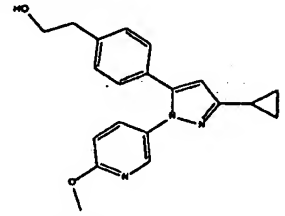
mp. 111-112℃

IR (KBr) : 3325, 2931, 1707, 1693, 1685, 1658, 1647, 1564, 1549, 1514cm-1

Mass (ESI+) : 335 (M+H)+

200MHz 1H NMR (DMSO-d6, d) : 0.69-0.77(2H, m), 0.86-0.96(2H, m), 1.93(1H, m), 2.69(2H, t, J=6.9 Hz), 3.53-3.64(2H, m), 3.76(3H, s), 4.64(1H, t, J=5.2 Hz), 6.28(1H, s), 6.92(2H, d, J=9.0 Hz), 7.05-7.19(6H, m)

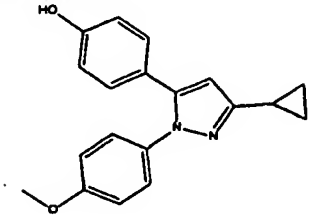
Example 33



(E0033)

P0033 was prepared from P0018 498.5mg in a similar manner to that of E0032.

Example 34



(E0034)

E0034 was prepared in a similar manner to that of E0032.

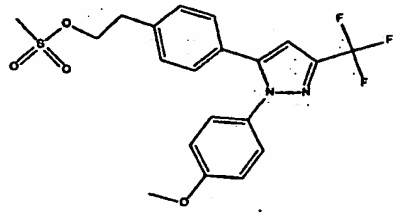
white powder

Mass (ESI+) : 306 (M+H)+

200MHz 1H NMR (DMSO-d6, d) :

0.67-0.76(2H, m), 0.84-0.94(2H, m), 1.91(1H, m), 3.76(3H, s), 6.18(1H, s), 6.68(2H, d, J=8.7 Hz), 6.91(2H, d, J=9.0 Hz), 6.98(2H, d, J=8.7 Hz), 7.12(2H, d, J=9.0 Hz), 9.63(1H, s)

Example 35

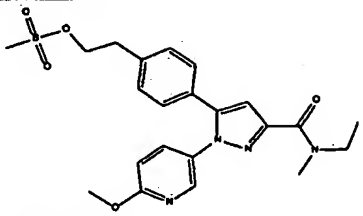


(E0035)

To a solution of E0014 (1.0g) and Et3N (0.6ml) in CH2Cl2 (20ml) was added dropwise methanesulfonyl chloride (0.26ml) under ice-cooling. After stirring for 1 hour, the reaction mixture was quenched with water and extracted with CHCl3. The organic layer was washed with water, dried over Na2SO4, filtered and evaporated to give 1.2g (99%) of crude E0035 as an off-white solid.

IR (film): 1513.9, 1469.5, 1351.9, 1240.0, 1166.7, 1130.1, 971.9, 835.0, 804.2cm-1.

Example 36



(E0036)

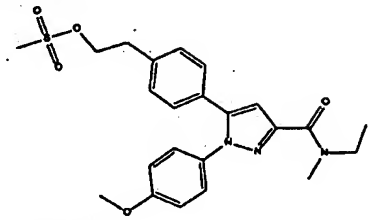
E0036 was prepared in a similar manner to that of E0035.

Mass (ESI+) : 459 (M+H)+

200MHz 1H NMR (DMSO-d6, d)

1.09-1.23(3H, m), 2.98,3.29(3H, s), 3.01(2H, t, J=6.6 Hz), 3.09(3H, s), 3.43-3.77(2H, m), 3.87(3H, s), 4.42(2H, t, J=6.6 Hz), 6.88-6.92(2H, m), 7.25(2H, d, J=8.3 Hz), 7.33(2H, d, J=8.3 Hz), 7.65-7.73(1H, m), 8.15(1H, d, J=2.6 Hz)

Example 37



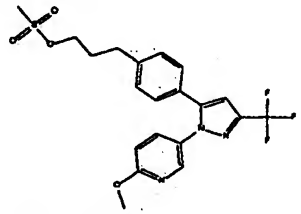
(E0037)

E0037 was prepared in a similar manner to that of E0035.

Mass (APCI+) : 458 (M+H)+

200MHz 1H NMR (DMSO-d6, d) : 1.05-1.25(3H, m), 2.96-3.03(2H, m), 2.98,3.29(3H, s), 3.08(3H, s), 3.40-3.85(2H, m), 3.78(3H, s), 4.42(2H, t, J=6.6 Hz), 6.86,6.88(1H, s), 6.98(2H, d, J=8.9 Hz), 7.18-7.32(6H, m)

Example 38



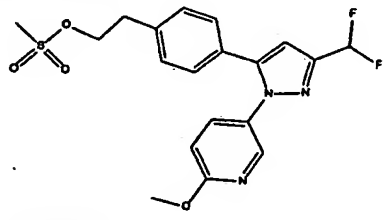
(No. E0038)

E0038 was prepared in a similar manner to that of E0035.

Mass (ESI+) : 456 (M+H)+

200MHz 1H NMR (DMSO-d6, d) : 1.89-2.04(2H, m), 2.52-2.73(2H, m), 3.16(3H, s), 3.88(3H, s), 4.19(2H, t, J=6.3 Hz), 6.92(1H, d, J=8.9 Hz), 7.18(1H, s), 7.21-7.31(4H, m), 7.76(1H, dd, J=2.6,8.9 Hz), 8.19(1H, d, J=2.6 Hz)

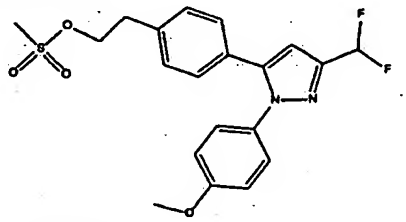
Example 39



(E0039)

E0039 was obtained according to a similar manner to that of E0035.

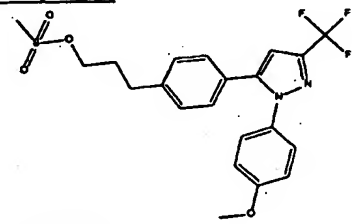
Example 40



(E0040)

E0040 was obtained according to a similar manner to that of E0035.

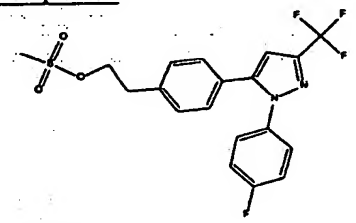
Example 41



(E0041)

This compound was obtained according to a similar manner to that of E0035.

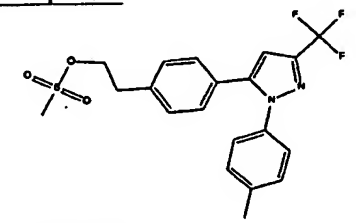
Example 42



(E0042)

This compound was obtained according to a similar manner to that of E0035.

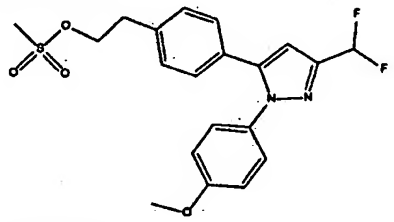
Example 43



(E0043)

This compound was obtained according to a similar manner to that of E0035.

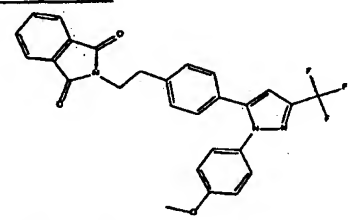
Example 44



(E0044)

This compound was obtained according to a similar manner to that of E0035.

Example 45

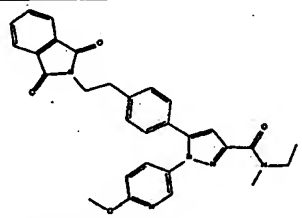


(E0045)

A mixture of E0035 (900mg) and potassium phthalimide (454mg) in DMF (18ml) was stirred at 60oC for 3.0 hours. After addition of water, the reaction mixture was extracted with EtOAc and washed twice with water and with brine. The organic layer was dried over Na2SO4 ,filtered and evaporated under reduced pressure. The residue was column chromatographed on silica gel (50ml) to give 930mg (93%) of E0045 as a powder.

IR (film): 1772.3, 1712.5, 1240.0, 1160.9, 1130.1cm-1.

Example 46



(E0046)

E0046 was prepared from E0036 in a similar manner to that of E0045.

amorphous powder

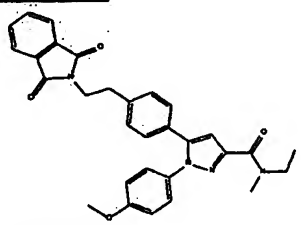
Mass (ESI+) : 510 (M+H)+

200MHz 1H NMR (DMSO-d6, d) :

1.08-1.22(3H, m), 2.89-2.98(2H, m), 2.98,3.27(3H, s), 3.48,3.70(2H, q, J=7.1,6.9 Hz),

3.82(2H, t, J=7.3 Hz), 3.88(3H, s), 6.83-6.88(2H, m), 7.23(2H, d, J=8.7 Hz), 7.18(2H, d, J=8.7 Hz), 7.53-7.63(1H, m), 7.79-7.89(4H, m), 8.15(1H, d, J=2.6 Hz)

Example 47



(E0047)

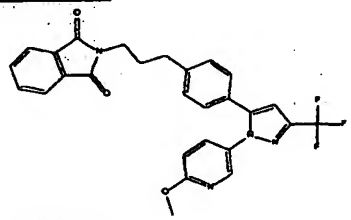
E0047 was prepared from E0037 in a similar manner to that of E0045.

amorphous powder

Mass (ESI+) : 509 (M+H)+

200MHz 1H NMR (DMSO-d6, d) : 1.12,1.18(3H, t, J=7.0,7.1 Hz), 2.92(2H, t, J=7.0 Hz), 2.97,3.28(3H, s), 3.47,3.71(2H, q, J=7.1,7.0 Hz), 3.78(3H, s), 3.81(2H, t, J=7.0 Hz), 6.82,6.84(1H, s), 6.94(2H, d, J=9.0 Hz), 7.11-7.20(6H, m), 7.79-7.89(4H, m)

Example 48



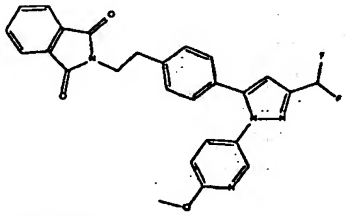
(E0048)

E0048 was prepared from E0038 in a similar manner to that of E0045.

Mass (ESI+) : 507 (M+H)+

200MHz 1H NMR (DMSO-d6, d) : 1.82-1.97(2H, m), 2.59-2.67(2H, m), 3.60(2H, t, J=7.0 Hz), 3.88(3H, s), 6.91(1H, d, J=8.8 Hz), 7.14(1H, s), 7.20(2H, d, J=8.5 Hz), 7.26(2H, d, J=8.5 Hz), 7.73(1H, dd, J=8.8,2.8 Hz), 7.78-7.89(4H, m), 8.17(1H, d, J=2.8 Hz)

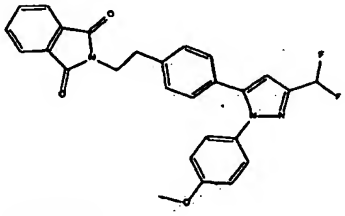
Example 49



(E0049)

This compound was obtained according to a similar manner to that of E0045.

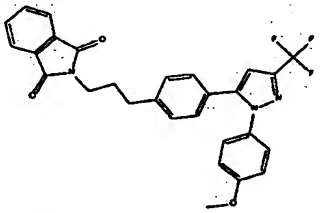
Example 50



(E0050)

This compound was obtained according to a similar manner to that of E0045.

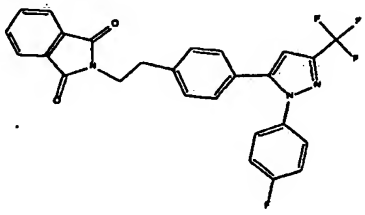
Example 51



(E0051)

This compound was obtained according to a similar manner to that of E0045.

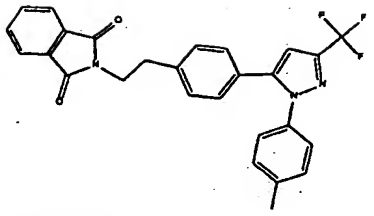
Example 52



(E0052)

This compound was obtained according to a similar manner to that of E0045.

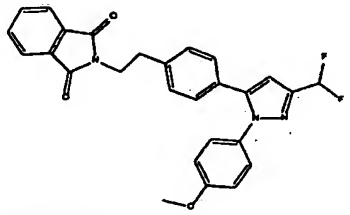
Example 53



(E0053)

This compound was obtained according to a similar manner to that of E0045.

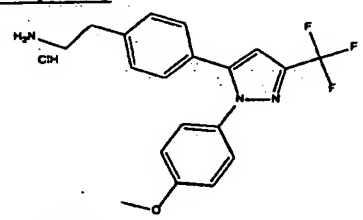
Example 54



(E0054)

This compound was obtained according to a similar manner to that of E0045.

Example 55

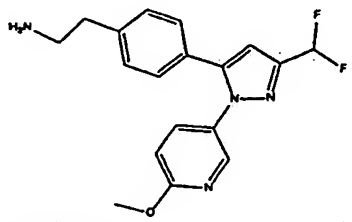


(E0055)

To a solution of E0045 (800mg) in CH3CN (10ml) was added hydrazine hydroxide (87ul) at room temperature. After stirring for 1 hour, the reaction mixture was filtered and evaporated. After addition of dichloromethane, the mixture was stirred for an hour, filtered and evaporated. The residue was treated with 4NHCl/EtOAc to give 518mg (80%) of E0055.

IR (Film); 3403.74, 1610.27, 1511.92, 1467.56, 1238.08, 1160.94, 1130.08, 1027.87, 975.80, 836.96, 806.10cm-1.

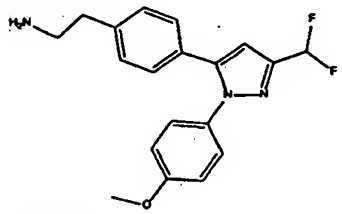
Example 56



(E0056)

This compound was obtained according to a similar manner to that of E0055.

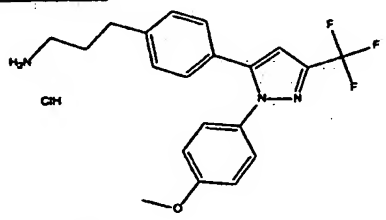
Example 57



(E0057)

This compound was obtained according to a similar manner to that of E0055.

Example 58

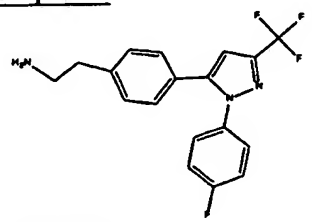


(E0058)

This compound was obtained according to a similar manner to that of E0055.

IR (film): 3428.8, 1511.9, 1467.6, 1238.1, 1160.9, 1132.0cm-1.

Example 59



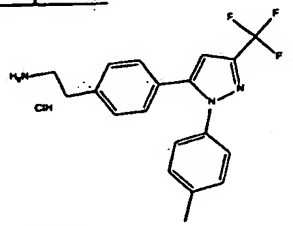
(E0059)

This compound was obtained according to a similar manner to that of E0055.

IR (film): 3371.0, 1511.9, 1471.4, 1272.8, 1230.4, 1160.9, 1133.9, 975.8, 842.7,

810.0cm-1.

Example 60



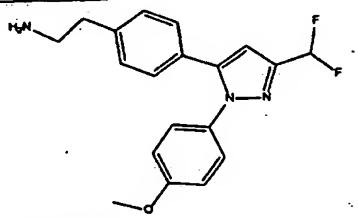
(E0060)

This compound was obtained according to a similar manner to that of E0055.

mp: 163.1-165.1oC

IR (film): 2973.7, 1511.9, 1471.4, 1236.2, 1159.0, 1133.9cm-1.

Example 61

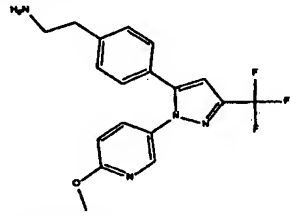


(E0061)

This compound was obtained according to a similar manner to that of E0055.

IR(film): 3369.0, 1604.5, 1513.9, 1459.9, 1251.6, 1172.5, 1083.8, 1029.8,837.0, 800.3 cm-1.

Example 62



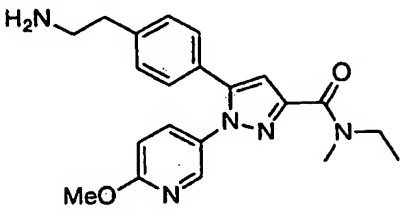
(E0062)

To a solution of E0343 (1.08 g) in acetonitril (15 ml) was added hydrazine monohydrate (0.53 ml). After stirring at 60℃ overnight, the mixture was filtered. And the filtrate was evaporated to give E0062 as an orange oil (814 mg, 102%).

NMR(CDCl3), 2.76(2H, t, J=6.5 Hz), 2.98(2H, t, J=6.5 Hz), 3.94(3H, s), 6.73(1H, s), 6.76(1H, d, J=8.9 Hz), 7.22-7.12(4H, m), 7.57(1H, dd, J=8.9, 2.7 Hz), 8.09(1H, d, J=2.7

Hz).
MS(ESI+);363.3(MH+).

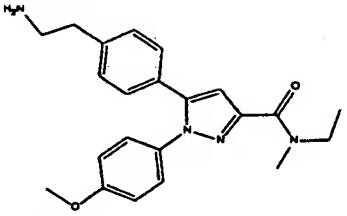
Example 63



(E0063)

E0063 was prepared from E0046 in a similar manner to that of E0062.
Mass (ESI+) : 380 (M+H)+
200MHz 1H NMR (DMSO-d6, d) :
1.91-1.23(3H, m), 2.59-2.79(4H, m), 2.98,3.28(3H, s), 3.48,3.71(2H, q, J=7.2,7.0 Hz), 3.87(3H, s), 6.86-6.93(2H, m), 7.16-7.26(4H, m), 7.64-7.73(1H, m), 8.15(1H, d, J=2.5 Hz)

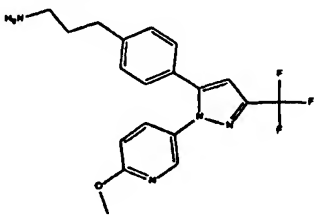
Example 64



(E0064)

E0064 was prepared from E0047 in a similar manner to that of E0062.
Mass (ESI+) : 379 (M+H)+
200MHz 1H NMR (DMSO-d6, d) :
1.08-1.22(3H, m), 2.57-2.78(4H, m), 2.97,3.29(3H, s), 3.48,3.72(2H, q, J=7.2,7.0 Hz), 3.78(3H, s), 6.83,6.85(1H, s), 6.98(2H, d, J=8.9 Hz), 7.06-7.26(6H, m)

Example 65



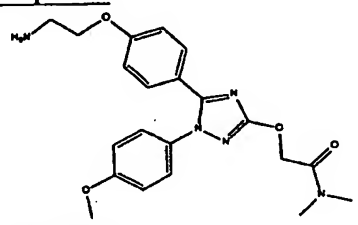
(E0065)

E0065 was prepared from E0048 in a similar manner to that of E0062.

Mass (ESI+) : 377 (M+H)+

200MHz 1H NMR (DMSO-d6, d) : 1.54-1.69(2H, m), 2.49-2.64(4H, m), 3.88(3H, s), 6.92(1H, d, J=8.7 Hz), 7.17(1H, s), 7.22(4H, s), 7.75(1H, dd, J=8.7,2.6 Hz), 8.18(1H, d, J=2.6 Hz)

Example 66



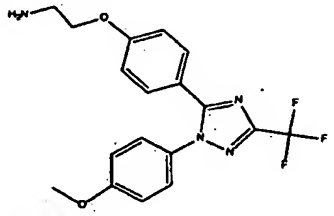
(E0066)

E0066 was obtained according to a similar manner to that of E0062.

1H NMR (CDCl3, ppm) d 3.00(3H,), 2.99-3.17(5H,), 3.84(3H,), 3.98(2H, t, J=5.1 Hz), 5.01(2H, s), 6.75-6.98(4H, m), 7.18-7.33(2H, m), 7.35-7.47(2H, m),

MS (ESI, m/e) 412(M+1)

Example 67



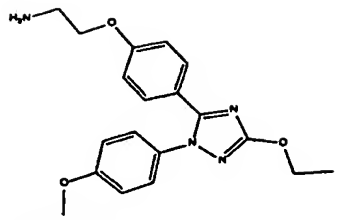
(E0067)

E0067 was obtained according to a similar manner to that of E0062.

1H NMR (CDCl3, ppm) d 3.09(2H, t, J=5.1 Hz), 3.87(3H, s), 4.00(2H, t, J=5.1 Hz), 6.79-7.10(4H, m), 7.22-7.58(4H, m),

MS (ESI, m/e) 379(M+1)

Example 68



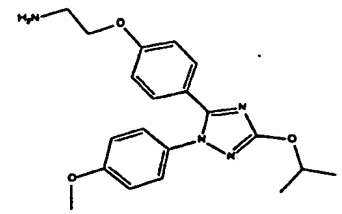
(E0068)

E0068 was obtained according to a similar manner to that of E0062.

1H NMR (CDCl3, ppm) d 1.45(3H, t, J=7.0 Hz), 3.07(2H, t, J=5.1 Hz), 3.84(3H, s), 3.98(2H, t, J=5.1 Hz), 4.39(2H, q, J=7.0 Hz), 6.78-6.98(4H, m), 7.22-7.33(2H, m), 7.35-7.49(2H, m),

MS (ESI, m/e) 355(M+1)

Example 69



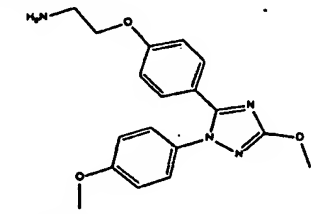
(E0069)

E0069 was obtained according to a similar manner to that of E0062.

1H NMR (CDCl3, ppm) d 1.43(6H, d, J=6.2 Hz), 3.08(2H, t, J=5.1 Hz), 3.84(3H, s), 3.98(2H, t, J=5.1 Hz), 5.02(1H, 7th, J=6.1 Hz), 6.75-7.00(4H, m), 7.20-7.35(2H, m), 7.35-7.49(2H, m),

MS (ESI, m/e) 369(M+1)

Example 70



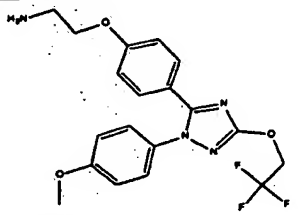
(E0070)

E0070 was obtained according to a similar manner to that of E0062.

1H NMR (CDCl3, ppm) d 3.08(2H, t, J=5.2 Hz), 3.84(3H, s), 3.98(2H, t, J=5.1 Hz), 4.05(3H, s), 6.79-7.00(4H, m), 7.20-7.35(2H, m), 7.35-7.49(2H, m),

MS (ESI, m/e) 341(M+1)

Example 71



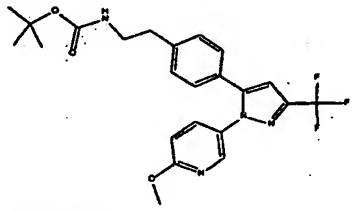
(E0071)

E0071 was obtained according to a similar manner to that of E0062.

1H NMR (CDCl3, ppm) d 3.08(2H, t, J=5.1 Hz), 3.85(3H, s), 3.99(2H, t, J=5.1 Hz), 4.74(2H, q, J=8.3 Hz), 6.78-7.00(4H, m), 7.18-7.35(2H, m), 7.35-7.48(2H, m),

MS (ESI, m/e) 409(M+1)

Example 72



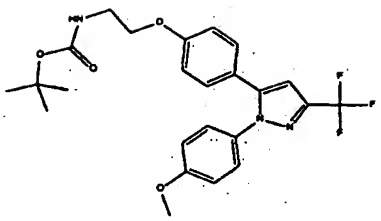
(E0072)

To a solution of E0062 (180 mg) in tetrahydrofuran (2 ml) was added triethylamine (0.242 ml) and t-butoxycarbonyl anhydride (325 mg) at room temperature. After stirring at room temperature overnight, the mixture was quenched with water and extracted with ethyl acetate (x3). The organic layer was washed with hydrogen chloride aqueous solution (1N), saturated sodium hydrogen carbonate aqueous solution, and brine, dried over magnesium sulfate, and evaporated to give oil, which was purified with column chromatography (SiO2 25 ml, 20% ethyl acetate/hexane) to give E0072 as an oil (224 mg , 97.5%).

NMR(CDCl3); 1.35(9H, s), 2.69(2H, t, J=7.7 Hz), 3.09-3.19(2H, m), 3.88(3H, s), 6.91(1H, d, J=8.8 Hz), 7.17(1H, s), 7.18-7.27(4H, m), 7.75(1H, dd, J=8.8, 2.7 Hz), 8.19(1H, d, J=2.7 Hz).

MS(ESI+); 485.2(M+Na).

Example 73



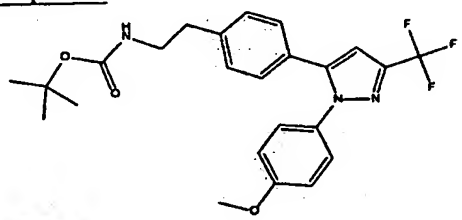
(E0073)

This compound was obtained according to a similar manner to that of E0072.

NMR(CDCl3), 1.45(9H, s), 3.49-3.57(2H, m), 3.82(3H, s), 4.01(2H, t, J=5.1 Hz), 6.67(1H, s), 6.82(2H, d, J=8.7 Hz), 6.87(2H, d, J=9.0 Hz), 7.13(2H, d, J=8.7 Hz), 7.22(2H, d, J=9.0 Hz).

MS(ESI+), 500.2(M+Na).

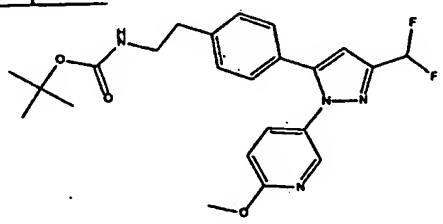
Example 74



(E0074)

A mixture of E0055 (650mg) , Boc2O (428mg) and 1NNaOH (3.3ml) in THF (20ml) was stirred at room temperature for 15 hours. Water and EtOAc was added and the aqueous layer was separated and extracted with EtOAc. The combined organic layer was washed with sat NaHCO3, water and brine, dried over NA2SO4, filtered and evaporated under reduced pressure. The residue was column chromatographed on silica gel (Hex/EtOAc) to give 700mg (93%) of E0074 as an oil.

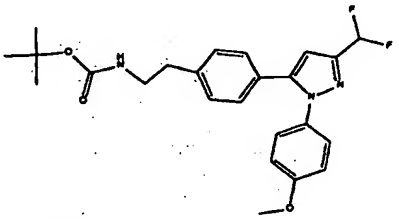
Example 75



(E0075)

This compound was obtained according to a similar manner to that of E0074.

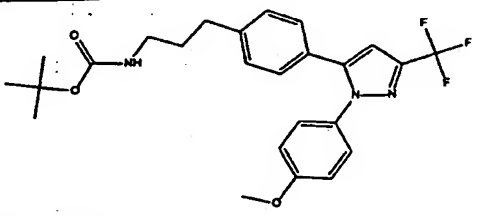
Example 76



(E0076)

This compound was obtained according to a similar manner to that of E0045.

Example 77

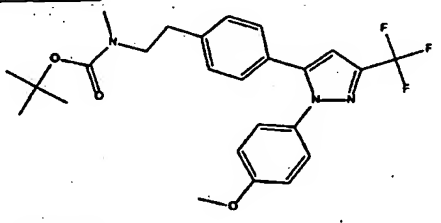


(E0077)

This compound was obtained according to a similar manner to that of E0074.

IR (film): 1702.8, 1513.9, 1241.9, 1164.8, 1132.0cm-1.

Example 78



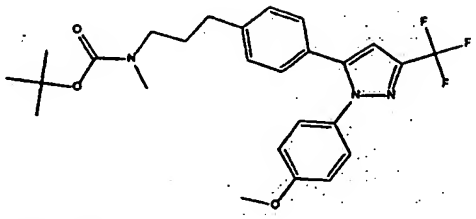
(E0078)

To a solution of E0074 (200mg) and MeI (0.14ml) in THF (20ml) was added portionwise NaH (35mg) at room temperature. Then the reaction mixture was heated at 70oC for 1 hour. Almost no reaction.

MeI (0.3ml) and NaH (40mg) was added, and DMF was added.

The mixture was stirred at 70oC for 12 hours, and then cooled, quenched with water. The aqueous layer was extracted twice with EtOAc. The combined organic layer was washed with water and brine, dried over MgSO4, filtered and evaporated. The residue was column chromatographed on silica gel to give 151mg (73%) of E0078 as an oil.

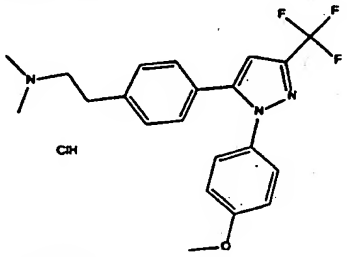
Example 79



(E0079)

This compound was obtained according to a similar manner to that of E0078.

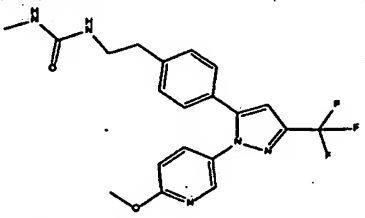
Example 80



(E0080)

To a mixture of E0055 (150mg) and HCHO (46ul) in Et3N (53ul) and CH3CN (5ml) was added portionwise NaBH(OAc)2 (240mg) at room temperature. After stirring for 15 hours, the mixture was quenched with water and extracted three times with EtOAc. The combined organic layer was washed with water and brine, dried over Na2SO4, filtered and evaporated under reduced pressure. The residue was column chromatographed on silica gel (CHCl3/MeOH) and treated with 4NHCl/dioxane to give 108mg (70%) of E0080.

Example 81



(E0081)

Methylisocyanate 36.2mg was added to a solution of E0199.3mg and triethylamine 48.6mg in CH2Cl2 2ml under ice bath cooling. The reaction mixture was stirred at same temperature for 1hour and concentrated in vacuo. The residue was partitioned between AcOEt and 1M HCl. The organic layer was washed with saturated aqueous sodium bicarbonate solution and saturated aqueous sodium chloride solution, dried over

magnesium sulfate, and concentrated in vacuo. The residue was recrstallized from AcOEt-n-hexane. Obtained powder was dissolved in CHCl3 and further purified by preparative thin layer silica gel chromatography developed by MeOH / CHCl3 = 10%. The seaparated silica gel was extracted with 10% MeOH/CHCl3 and the solvent was evaporated in vacuo. The residual solid was collected and washed with diisopropyl ether to give E0081 (101.3mg) as a white powder.

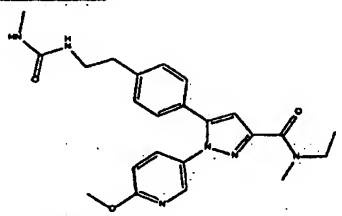
mp. 149℃

IR (KBr) : 3348, 2947, 2885, 1626, 1583, 1529, 1500cm-1

Mass (ESI+) : 420 (M+H)+

200MHz 1H NMR (DMSO-d6, d) : 2.49-2.53(3H, overlapping), 2.64-2.72(2H, m), 3.15-3.26(2H, m), 3.88(3H, s), 5.72(1H, q, J=4.5 Hz), 5.89(1H, t, J=5.7 Hz), 6.92(1H, d, J=8.8 Hz), 7.17(1H, s), 7.24(4H, s), 7.76(1H, dd, J=2.7, 8.8 Hz), 8.19(1H, d, J=2.7 Hz)

Example 82



(E0082)

E0082 80.7mg was prepared from E0063 in a similar manner to that of E0081.

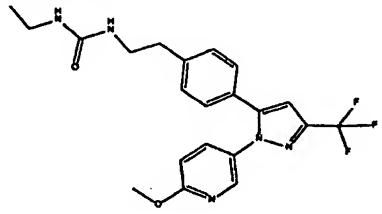
amorphous powder

IR (neat) : 3350, 2950, 2930, 1707, 1691, 1674, 1645, 1641, 1622, 1614, 1566, 1549, 1533, 1510cm-1

Mass (ESI+) : 437 (M+H)+

200MHz 1H NMR (DMSO-d6, d) : 1.09-1.23(3H, m), 2.49-2.54(3H, overlapping), 2.67(2H, t, J=7.2 Hz), 2.98,3.28(3H, s), 3.15-3.28(2H, m), 3.48,3.71(2H, q, J=6.8,6.9 Hz), 3.88(3H, s), 5.73(1H, q, J=4.6 Hz), 5.90(1H, t, J=5.6 Hz), 6.86-6.93(2H, m), 7.22(4H, s), 7.64-7.73(1H, m), 8.15(1H, d, J=2.6 Hz)

Example 83



(E0083)

E0083 was prepared from E0199 in a similar manner to that of E0081.

white powder

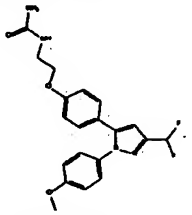
mp. 155-157℃

IR (KBr) : 3336, 2968, 1707, 1693, 1674, 1621, 1576, 1533cm-1

Mass (ESI+) : (M+H)+

200MHz 1H NMR (DMSO-d6, d) : 0.96(3H, t, J=7.1 Hz), 2.64-2.72(2H, m), 2.91-3.05(2H, m), 3.15-3.26(2H, m), 3.88(3H, s), 5.76-5.84(2H, m), 6.92(1H, d, J=8.8 Hz), 7.17(1H, s), 7.24(4H, s), 7.76(1H, dd, J=8.8,2.7 Hz), 8.19(1H, d, J=2.7 Hz)

Example 84

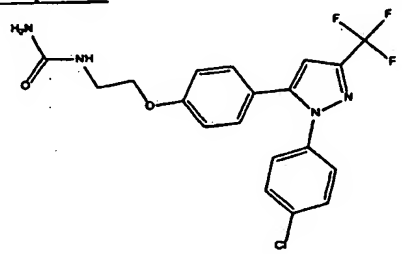


(E0084)

This compound was obtained according to a similar manner to that of E0081.

IR (film): 3343.9, 1658.5, 1608.3, 1513.9, 1457.9, 1249.6, 1029.8, 836.9 cm-1.

Example 85

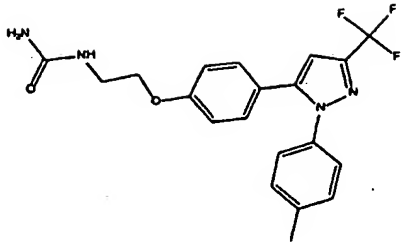


(E0085)

This compound was obtained according to a similar manner to that of E0081.

IR (Film): 1659.0, 1608.8, 1554.8, 1485.4, 1470.0, 1240.4, 1165.1, 1134.3, 1097.6, 835.3cm-1.

Example 86

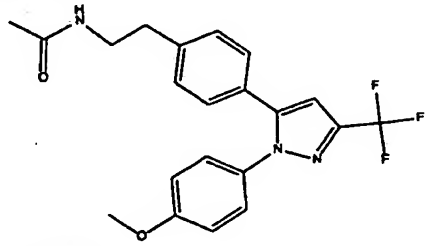


(E0086)

This compound was obtained according to a similar manner to that of E0081.

IR (film): 3249.8, 1658.5, 1608.3, 1554.3, 1469.5, 1240.0, 1164.8, 1133.9, 1097.3, 975.8, 835.0 cm-1.

Example 87



(E0087)

AcCl 23.3mg was added to E0055 (107.4mg) and triethylamine 68.3mg in CH2Cl2 2ml with cooling in an ice bath. After stirring at same temperature for 1hour, the reaction mixture was concentrated in vacuo. The residue was partitioned between AcOEt and 1M HCl. The organic layer was washed with saturated aqueous sodium bicarbonate solution and saturated aqueous sodium chloride solution, dried over magnesium sulfate, and concentrated in vacuo. The residual solid were collected and washed with diisopropyl ether to give E0087 (84mg) as a white powder.

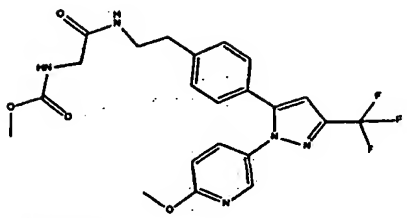
mp. 79-80℃

IR (KBr) : 3307, 3221, 3093, 2964, 1689, 1639, 1554, 1514cm-1

Mass (ESI+) : 404 (M+H)+

200MHz 1H NMR (DMSO-d6, d) : 1.76(3H, s), 2.65-2.73(2H, m), 3.18-3.31(2H, m), 3.79(3H, s), 6.99(2H, d, J=8.9 Hz), 7.12(1H, s), 7.20(4H, s), 7.28(2H, d, J=8.9 Hz), 7.92(1H, t, J=5.4 Hz)

Example 88



(E0088)

E0088 (143.4mg) was prepared from E0137 (155.3mg), methyl chloroformate 35.8mg, and triethylamine 105mg in a similar manner to that of E0087.

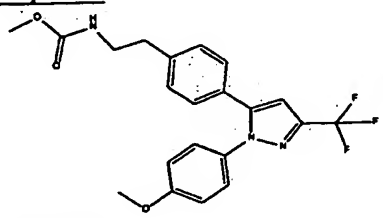
amorphous powder

IR (neat) : 3319, 2954, 1718, 1711, 1668, 1660, 1612, 1545, 1533, 1500cm-1

Mass (ESI+) : 178 (M+H)+

200MHz 1H NMR (DMSO-d6, d) : 2.67-2.75(2H, m), 3.22-3.33(2H, m), 3.50-3.60(2H, overlapping), 3.53(3H, s), 3.88(3H, s), 6.92(1H, d, J=8.8 Hz), 7.18(1H, s), 7.24(4H, s), 7.28(1H, t, J=6 Hz), 7.75(1H, dd, J=2.7,8.8 Hz), 7.94(1H, t, J=5.6 Hz), 8.19(1H, d, J=2.7 Hz)

Example 89



(E0089)

E0089 (59.3mg) was prepared from E0055 (96.2mg), methyl chloroformate 25.1mg and triethylamine 61.2mg in a similar manner to that of E0087.

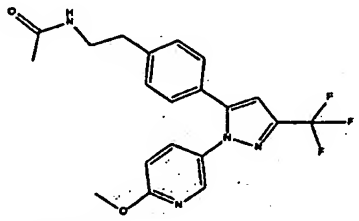
mp. 78-80℃

IR (KBr) : 3352, 1739, 1695, 1658, 1647, 1549, 1514cm-1

Mass (ESI+) : 420 (M+H)+

200MHz 1H NMR (DMSO-d6, d) : 2.66-2.74(2H, m), 3.14-3.25(2H, m), 3.49(3H, s), 3.79(3H, s), 6.99(2H, d, J=8.9 Hz), 7.12(1H, s), 7.12-7.32(1H, m), 7.20(4H, s), 7.28(2H, d, J=8.9 Hz)

Example 90



(E0090)

E0090 (63.4mg) was prepared from E0062 (113.6mg), acetyl chloride 29.5mg, and triethylamine 41.2mg in a similar manner to that of E0087.

white powder

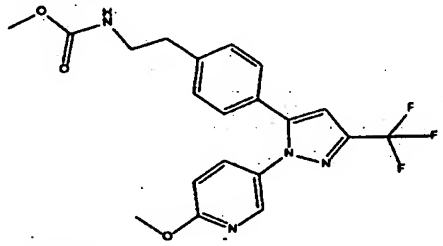
mp.97-98℃

IR (KBr) : 3311, 2956, 1674, 1641, 1543, 1500cm-1

Mass (ESI+) : 405 (M+H)+

200MHz 1H NMR (DMSO-d6, d) : 1.76(3H, s), 2.66-2.74(2H, m), 3.19-3.30(2H, m), 3.88(3H, s), 6.92(1H, d, J=8.8 Hz), 7.18(1H, s), 7.24(4H, s), 7.75(1H, dd, J=8.8,2.6 Hz), 7.92(1H, t, J=5.3 Hz), 8.19(1H, d, J=2.6 Hz)

Example 91



(E0091)

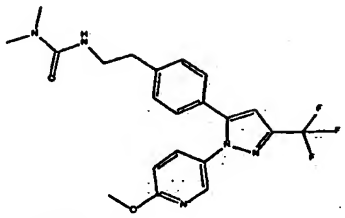
E0091 was prepared from E0062 in a similar manner to that of E0087 .

IR (neat) : 3338, 3020, 2951, 1716, 1610, 1527, 1500cm-1

Mass (ESI+) : 421 (M+H)+

200MHz 1H NMR (DMSO-d6, d) : 2.67-2.75(2H, m), 3.14-3.25(2H, m), 3.49(3H, s), 3.88(3H, s), 6.92(1H, d, J=8.9 Hz), 7.15-7.35(5H, m), 7.18(1H, s), 7.75(1H, dd, J=2.7,8.9 Hz), 8.19(1H, d, J=2.7 Hz)

Example 92



(E0092)

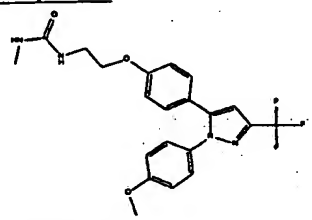
E0092 was prepared from E0199 in a similar manner to that of E0087.

IR (neat) : 3352, 2939, 1691, 1639, 1533, 1500cm-1

Mass (ESI+) : 434 (M+H)+

200MHz 1H NMR (DMSO-d6, d) : 2.67-2.74(2H, m), 2.74(6H, s), 3.15-3.26(2H, m), 3.88(3H, s), 6.34(1H, t, J=5.4 Hz), 6.92(1H, d, J=8.9 Hz), 7.17(1H, s), 7.23(4H, s), 7.75(1H, dd, J=8.9,2.7 Hz), 8.19(1H, d, J=2.7 Hz)

Example 93



(E0093)

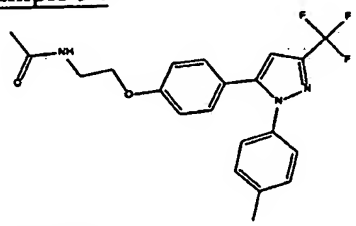
This compound was obtained according to a similar manner to that of E0092.

NMR(CDCl3); 2.78(3H, d, J=5.0 Hz), 3.56-3.64(2H, m), 3.82(3H, s), 4.03(2H, t, J=5.1 Hz), 4.2-4.4(1H, m, NH), 4.6-4.9(1H, m, NH), 6.67(1H, s), 6.80-6.91(4H, m), 7.13(2H, d, J=8.8 Hz), 7.22(2H, d, J=9.0 Hz).

MS(ESI+).457.1(M+Na).

IR(NBr), 1627.6cm-1

Example 94

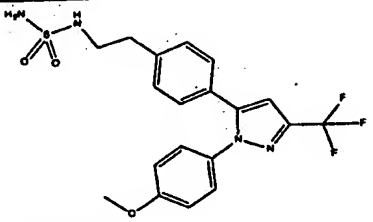


(E0094)

This compound was obtained according to a similar manner to that of E0087.

IR (film): 3299.6, 1658.5, 1550.5, 1515.8, 1467.6, 1240.0, 1164.8, 1132.0, 975.8, 829.2, 755.9 cm-1.

Example 95



(E0095)

E0055 250mg was suspended in AcOEt 5ml and was partitioned between AcOEt and saturated aqueous sodium bicarbonate solution. The organic layer was washed with aqueous sodium chloride solution, dried over magnesium sulfate, and concentrated in vacuo. The residue was dissolved in dimethoxyethane 5ml, sulfamide 181mg was added and refluxed for 2days. The reacion mixture was concentrated in vacuo, and the residue was purified by silica gel column chromatography eluted with MeOH / CHCl3 = 1%, 2%, then 3%. Obtained amorphous powder was crystallized from EtOH-diisopropyl ehter to give E0095 153mg as a white powder.

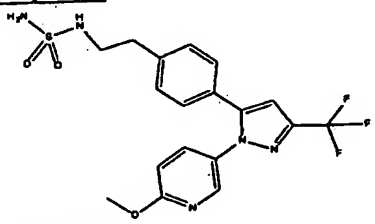
mp. 127-128℃

IR (KBr) : 3357, 1707, 1693, 1647, 1564, 1549, 1529, 1514cm-1

Mass (ESI+) : 441 (M+H)+

400MHz 1H NMR (DMSO-d6, d) : 2.76-2.80(2H, m), 3.06-3.11(2H, m), 3.79(3H, s), 6.53(2H, s), 6.53-6.61(1H, broad), 7.00(2H, d, J=8.9 Hz), 7.12(1H, s), 7.21(2H, d, J=8.5 Hz), 7.24(2H, d, J=8.5 Hz), 7.29(2H, d, J=8.9 Hz)

Example 96



(E0096)

E0096 was prepared from E0199 in a similar manner to that of E0095.

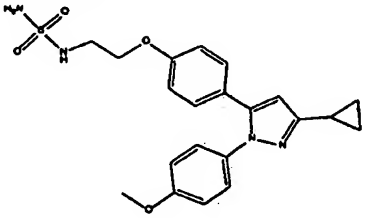
white powder

mp.114-115℃

IR (KBr) : 3489, 3469, 3458, 3435, 3425, 3398, 3363, 3280, 1647, 1500cm-1

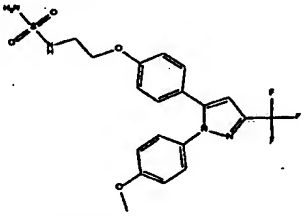
Mass (ESI+) : 442 (M+H)+
200MHz 1H NMR (DMSO-d6, d) : 2.75-2.83(2H, m), 3.00-3.20(2H, m), 3.88(3H, s), 6.45-6.67(3H, m), 6.92(1H, d, J=8.7 Hz), 7.18(1H, s), 7.21-7.31(4H, m), 7.76(1H, dd, J=2.6,8.7 Hz), 8.19(1H, d, J=2.6 Hz)

Example 97



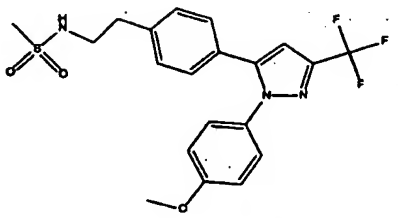
(E0097)
E0097 was prepared from E0233 in a similar manner to that of E0095.
white powder
mp. 142-143℃
IR (KBr) : 3415, 3323, 3111, 3093, 3010, 2962, 1614, 1516cm-1
Mass (ESI+) : 429 (M+H)+
200MHz 1H NMR (DMSO-d6, d) : 0.68-0.76(2H, m), 0.85-0.95(2H, m), 1.92(1H, m), 3.15-3.31(2H, m), 3.76(3H, s), 4.00-4.07(2H, m), 6.25(1H, 1), 6.60(2H, brs), 6.72(1H, brs), 6.86-6.96(4H, m), 7.10(2H, d, J=8.7 Hz), 7.13(2H, d, J=8.9 Hz)

Example 98



(E0098)
This compound was obtained according to a similar manner to that of E0095.
NMR(CDCl3), 3.50-3.59(2H, m), 3.82(3H, s), 4.14(2H, t, J=4.9 Hz), 6.68(1H, s), 6.80-6.90(4H, m), 7.15(2H, d, J=8.8 Hz), 7.22(2H, d, J=9.0 Hz).
IR(KBr); 1612, 1552cm-1.
MS(ESI+), 479.1(M+Na).

Example 99

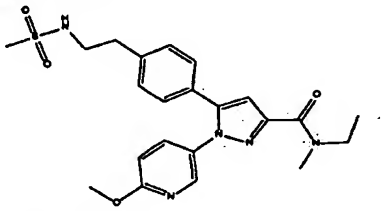


(E0099)

To a solution of E0055 (100mg) and Et3N (53ul) in CHCl3 (10ml) was added MsCl (29ul) at room temperature. After stirring for 1 hour, the reaction mixture was poured onto water and CHCl3. The aqueous layer was separated and extracted with CHCl3. The combined organic layer was washed with water and brine, dried over Na2SO4, filtered and evaporated under reduced pressure. The residue was column chromatographed on silica gel (50ml) and crystalized to give 75mg (68%) of E0099 as a powder.

IR (film): 3284.2, 1513.9, 1319.1, 1240.0, 1151.3, 973.9cm-1.

Example 100



(E0100)

E0100 was prepared from E0063 in a similar manner to that of E0099.

mp.137-138℃

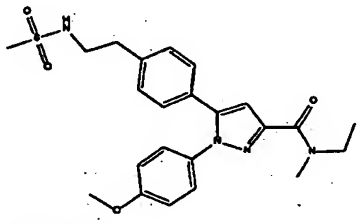
IR (KBr) : 3222, 1691, 1684, 1658, 1645, 1610, 1566, 1547, 1531cm-1

Mass (ESI+) : 458 (M+H)+

200MHz 1H NMR (DMSO-d6, d)

1.09-1.22(3H, m), 2.73-2.81(2H, m), 2.80(3H, s), 2.98,3.28(3H, s), 3.09-3.30(2H, m), 3.48,3.71(2H, q, J=7.0,6.8 Hz), 3.87(3H, s), 6.88-6.93(2H, m), 7.10(1H, brs), 7.22(2H, d, J=8.5 Hz), 7.28(2H, d, J=8.5 Hz), 7.64-7.73(1H, m), 8.15(1H, d, J=2.5 Hz)

Example 101



(E0101)

E0101 was prepared from E0064 in a similar manner to that of E0099.

mp.162-163℃

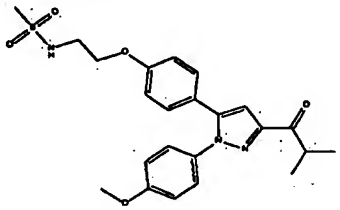
IR (KBr) : 3224, 1610, 1547, 1512cm-1

Mass (ESI+) : 457 (M+H)+

200MHz 1H NMR (DMSO-d6, d) :

1.08-1.22(3H, m), 2.76(2H, t, J=7.2 Hz), 2.80(3H, s), 2.98,3.29(3H, s), 3.12-3.23(2H, m), 3.48,3.73(2H, q, J=7.2,6.9 Hz), 3.78(3H, s), 6.84,6.87(1H, s), 6.98(2H, d, J=9.0 Hz), 7.09(1H, t, J=5.7 Hz), 7.16-7.26(6H, m)

Example 102



(E0102)

E0102 was prepared from E0139 in a similar manner to that of E0099.

white powder,

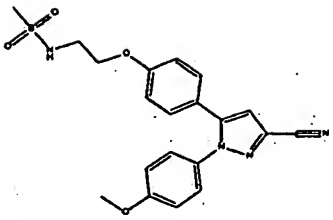
mp. 155℃

IR (KBr) : 3265, 2974, 2937, 1682, 1612, 1512cm-1

Mass (ESI+) : 458 (M+H)+

200MHz 1H NMR (DMSO-d6, d) : 1.15(6H, d, J=6.8 Hz), 2.94(3H, s), 3.27-3.36(2H, m), 3.68(1H, m), 3.79(3H, s), 4.03(2H, t, J=5.5 Hz), 6.93(2H, d, J=8.8 Hz), 6.98(1H, s), 7.00(2H, d, J=8.9 Hz), 7.19(2H, d, J=8.8 Hz), 7.28(2H, d, J=8.9 Hz), 7.17-7.30(1H, overlapping)

Example 103



(E0103)

E0103 was prepared from E0140 in a similar manner to that of E0099.

white powder

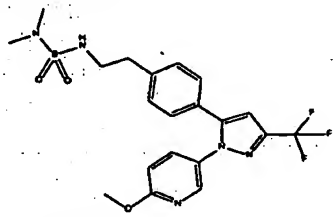
mp. 149-153℃

IR (KBr) : 3321, 1693, 1658, 1647, 1610, 1547, 1510cm-1

Mass (ESI+) : 413 (M+H)+

200MHz 1H NMR (DMSO-d6, d) : 2.93(3H, s), 3.27-3.35(2H, m), 3.79(3H, s), 4.03(2H, t, J=5.5 Hz), 6.95(2H, d, J=8.7 Hz), 7.01(2H, d, J=9.0 Hz), 7.18(2H, d, J=8.7 Hz), 7.28(2H, d, J=9.0 Hz), 7.31(1H, s), 7.15-7.31(1H, overlapping)

Example 104



(E0104)

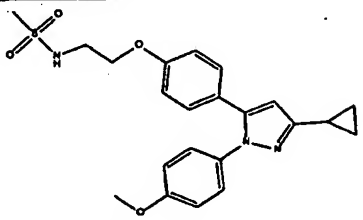
E0104 was prepared from E0199 in a similar manner to that of E0099.

IR (neat) : 3298, 2952, 2885, 1612, 1566, 1547, 1529cm-1

Mass (ESI+) : 470 (M+H)+

200MHz 1H NMR (DMSO-d6, d) : 2.56(6H, s), 2.71-2.79(2H, m), 3.07-3.17(2H, m), 3.88(3H, s), 6.92(1H, d, J=8.7 Hz), 7.18(1H, s), 7.19-7.30(5H, m), 7.77(1H, dd, J=8.7,2.6 Hz), 8.18(1H, d, J=2.6 Hz)

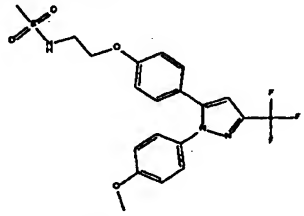
Example 105



(E0105)

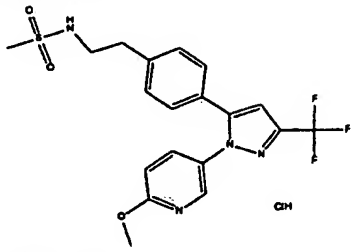
E0105 was prepared from E0233 in a similar manner to that of E0099.
white powder
mp. 166-168℃
IR (KBr) : 3093, 2964, 2873, 2854, 1614, 1516cm-1
Mass (ESI+) : 428 (M+H)+
200MHz 1H NMR (DMSO-d6, d) : 0.68-0.76(2H, m), 0.85-0.95(2H, m), 1.92(1H, m), 2.93(3H, s), 3.27-3.36(2H, m), 3.76(3H, s), 3.98-4.04(2H, m), 6.25(1H, s), 6.90(2H, d, J=8.7 Hz), 6.92(2H, d, J=8.9 Hz), 7.11(2H, d, J=8.7 Hz), 7.13(2H, d, J=8.9 Hz), 7.27(1H, t, J=5.8 Hz)

Example 106



(E0106)
This compound was obtained according to a similar manner to that of E0099.
MS(ESI+); 454.1(MH+).
IR(KBr); 1612.2, 1515.8cm-1.
NMR(CDCl3), 3.03(3H, s), 3.51-3.59(2H, m), 3.82(3H, s), 4.10(2H, t, J=4.9 Hz), 6.68(1H, s), 6.82(1H, d, J=8.7 Hz), 6.88(1H, d, J=8.9 Hz), 7.15(1H, d, J=8.7 Hz), 7.22(1H, d, J=8.9 Hz).

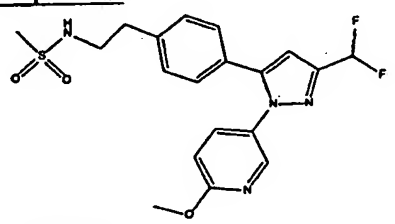
Example 107



(E0107)
This compound was obtained according to a similar manner to that of E0099.
NMR(DMSO-d6); 2.80(3H, s), 2.73-2.84(2H, m), 3.13-3.22(2H, m), 3.88(3H, s), 6.92(1H, d, J=9.0 Hz), 7.08-7.13(1H, m), 7.19(1H, s), 7.22-7.33(4H, m), 7.76(1H, dd, J=9.0, 2.6 Hz), 8.19(1H, d, J=2.6 Hz).

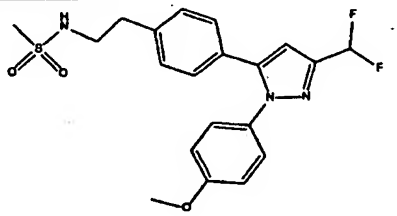
MS(ESI+),463.1(M+Na).
IR(KBr), 3136, 1614, 1554, 1144cm-1.

Example 108



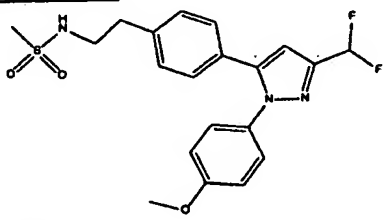
(E0108)
This compound was obtained according to a similar manner to that of E0099.

Example 109



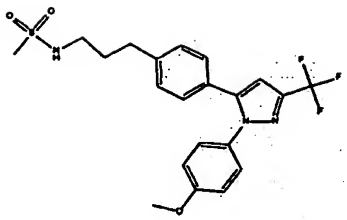
(E0109)
This compound was obtained according to a similar manner to that of E0099.
mp: 134.2-134.5℃
IR (film): 3284.2, 1610.3, 1513.9, 1457.9, 1321.0, 1251.6, 1151.3, 1083.8, 1031.7, 838.9, 802.2, 757.9 cm-1.

Example 110



(E0110)
This compound was obtained according to a similar manner to that of E0099.
IR (film): 3286.11, 1606.41, 1513.85, 1457.92, 1319.07, 1251.58, 1153.22, 1081.87, 1029.80, 836.955 cm-1.

Example 111

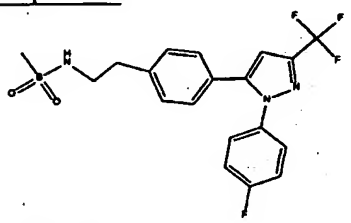


(E0111)

This compound was obtained according to a similar manner to that of E0099.

IR(film): 3284.2, 1513.9, 1317.1, 1240.0, 1153.2cm-1.

Example 112

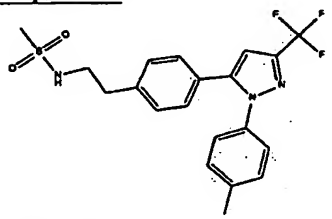


(E0112)

This compound was obtained according to a similar manner to that of E0099.

IR (film): 3286.1, 1511.9, 1321.0, 1230.4, 1155.2, 975.8, 842.7, 756.0cm-1.

Example 113

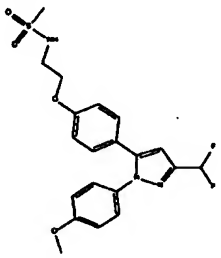


(E0113)

This compound was obtained according to a similar manner to that of E0099.

IR (film): 3284.2, 1511.9, 1469.5, 1321.0, 1236.2, 1153.2, 975.8, 821.5, 756.0cm-1.

Example 114

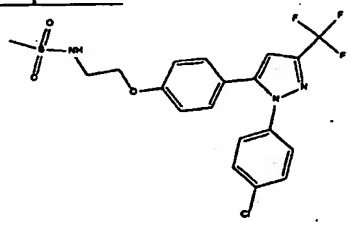


(E0114)

This compound was obtained according to a similar manner to that of E0099.

IR (film): 3289.9, 1612.2, 1513.9, 1322.9, 1251.6, 1155.1, 1085.7, 1029.8, 975.8, 836.9, 796.4 cm-1.

Example 115

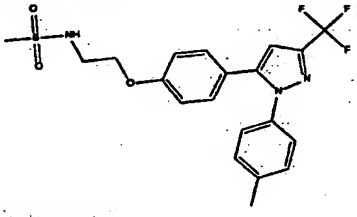


(E0115)

This compound was obtained according to a similar manner to that of E0099.

IR (film): 3266.8, 1612.2, 1469.5, 1321.0, 1240.0, 1153.2, 1097.3, 975.8, 835.0 cm-1.

Example 116

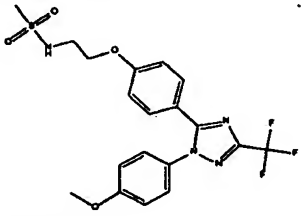


(E0116)

This compound was obtained according to a similar manner to that of E0099.

IR (film): 3288.0, 1612.2, 1322.9, 1240.0, 1153.2, 975.8, 946.9 cm-1.

Example 117



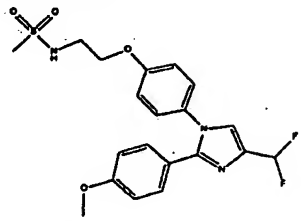
(E0117)

E0117 was obtained according to a similar manner to that of E0099.

1H NMR (CDCl3, ppm) d 3.02(3H, s), 3.55(2H, q, J=5.4 Hz), 3.87(3H, s), 4.11(2H, t, J=5.0 Hz), 4.81(1H, bt, J=5.8 Hz), 6.75-6.90(2H, m), 6.90-7.05(2H, m), 7.20-7.40(2H, m), 7.40-7.59(2H, m),

MS (ESI, m/e) 457(M+1)

Example 118

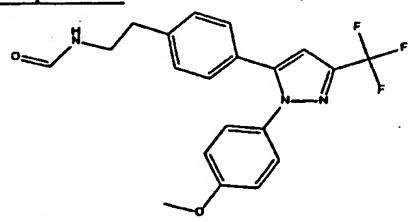


(E0118)

E0118 was obtained according to a similar manner to that of E0099.

MS (ESI, m/e) 438(M+1)

Example 119 (E-16, FR268698, S0203737, 白井 文幸)

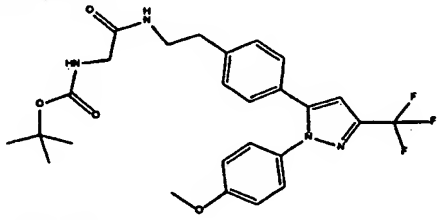


(E0119)

A mixture of E0055 (180mg), formic acid (38ul), and WSCD (155mg) in Et3N (0.3ml) and THF (5ml) was stirred at room temperature for 1 hour. After addition of water and EtOAc, the aqueous layer was separated and extracted twice with EtOAc. The combined organic layer was washed with 1NHCl, sat.NaHCO3, water and brine, dried over Na2SO4, filtered and evaporated under reduced pressure. The residue was column chromatographed on silica gel (Hex/EtOAc=2:1) to give 136mg (70%) of E0119 as a powder.

IR (film): 1670.1, 1513.9, 1238.1, 1160.9, 1130.1cm-1.

Example 120

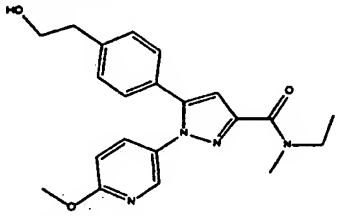


(E0120)

A mixture of E0055 (250mg), BocGly (132mg), WSCD (127mg) and HOBt (110mg)

in Et3N (114ul) and CH2Cl2 (30ml) was stirred at room temperature. After stirring for 15 hour, the reaction mixture was poured onto water and CHCl3. The aqueous layer was separated and extracted with CHCl3. The combined organic layer was washed with water and brine, dried over Na2SO4, filtered and evaporated under reduced pressure. The residue was column chromatographed on silica gel (50ml) and crystalized to give 325mg (99%) of E0120 as an oil.

Example 121



(E0121)

E0121 was prepared in a similar manner to that of E0120.

oil

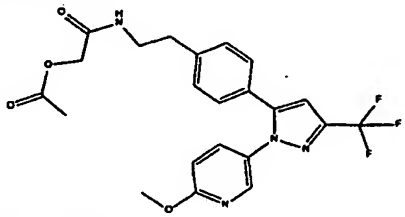
IR (neat) : 3431, 3421, 3404, 3400, 2939, 1614, 1570, 1547cm-1

Mass (ESI+) : 381(M+H)+

200MHz 1H NMR (DMSO-d6, d) : (回転異性体有り)

1.09-1.23(3H, m), 2.72(2H, t, J=6.9 Hz), 2.98,3.29(3H, s), 3.42-3.77(4H, m), 3.88(3H, s), 6.86-6.93(2H, m), 7.19(2H, d, J=8.5 Hz), 7.24(2H, d, J=8.5 Hz), 7.65-7.74(1H, m), 8.15(1H, d, J=2.6 Hz)

Example 122



(E0122)

E0122 was prepared from E0199 and acetoxyacetic acid in a similar manner to that of E0120.

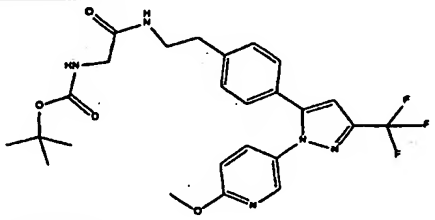
oil

Mass (ESI+) : 463(M+H)+

200MHz 1H NMR (DMSO-d6, d) : 2.07(3H, s), 2.69-2.77(2H, m), 3.24-3.33(2H, m), 3.88(3H, s), 4.40(2H, s), 6.92(1H, d, J=8.7 Hz), 7.18(1H, s), 7.24(4H, s), 7.75(1H, dd,

J=2.7,8.7 Hz), 8.10(1H, t, J=5.6 Hz), 8.19(1H, d, J=2.7 Hz)

Example 123



(E0123)

E0123 was prepared from E0199 and N-tert-butoxycarbonyl glycine in a similar manner to that of E0120 using N-methylmorpholine 55.8mg instead of triehtylamine.

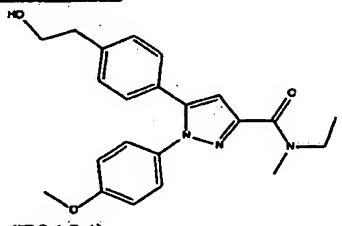
amorphous powder

IR (neat) : 3315, 1707, 1693, 1684, 1676, 1658, 1649, 1624, 1614, 1564, 1547, 1533, 1510, 1500cm-1

Mass (ESI+) : 520 (M+H)+

200MHz 1H NMR (DMSO-d6, d) : 1.37(9H, s), 2.67-2.75(2H, m), 3.22-3.33(2H, m), 3.47(2H, d, J=6.0 Hz), 3.88(3H, s), 6.80-7.00(1H, overlapping), 6.92(1H, d, J=8.8 Hz), 7.17(1H, s), 7.24(4H, s), 7.75(1H, dd, J=8.8,2.7 Hz), 7.86(1H, t, J=5.6 Hz), 8.19(1H, d, J=2.7 Hz)

Example 124



(E0124)

E0124 was prepared in a similar manner to that of E0120.

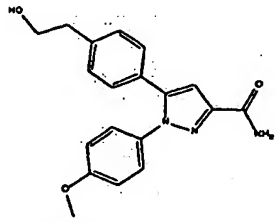
oil

IR (KBr) : cm-1 3329, 3313, 3303, 1620, 1564, 1547, 1512

Mass (ESI+) : 380 (M+H)+

200MHz 1H NMR (DMSO-d6, d): 1.08-1.22(3H, m), 2.71(2H, t, J=6.9 Hz), 2.97,3.29(3H, s), 3.42-3.78(4H, m), 3.78(3H, s), 4.65(1H, t, J=5.1 Hz), 6.82,6.85(1H, s), 6.98(2H, d, J=8.9 Hz), 7.12-7.27(6H, m)

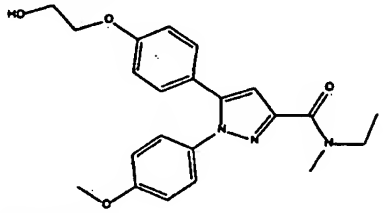
Example 125



(E0125)

E0125 was prepared in a similar manner to that of E0120.

Example 126



(E0126)

E0126 was prepared in a similar manner to that of E0120.

white powder

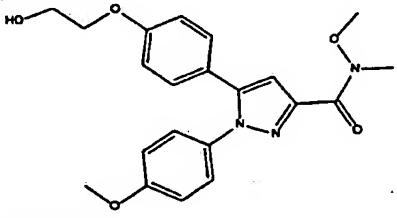
mp. 95-101℃

IR (KBr) : 3421, 1693, 1647, 1603, 1566, 1549, 1516cm-1

Mass (ESI+) : 396 (M+H)+

200MHz 1H NMR (DMSO-d6, d) : 1.08-1.22(3H, m), 2.97,3.29(3H, s), 3.42-3.74(4H, m), 3.78(3H, s), 3.95-4.00(2H, m), 4.86(1H, t, J=5.4 Hz), 6.78,6.81(1H, s), 6.91(2H, d, J=8.8 Hz), 6.98(2H, d, J=8.8 Hz), 7.16(2H, d, J=8.8 Hz), 7.23(2H, d, J=8.8 Hz)

Example 127



(E0127)

E0127 was prepared in a similar manner to that of E0120.

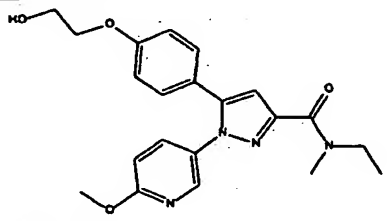
white powder

Mass (ESI+) : 398 (M+H)+

200MHz 1H NMR (DMSO-d6, d) : 3.38(3H, s), 3.65-3.74(2H, m), 3.77(3H, s), 3.78(3H,

s), 3.95-4.01(2H, m), 4.87(1H, t, J=5.4 Hz), 6.89(1H, s), 6.92(2H, d, J=8.8 Hz), 6.99(2H, s, J=8.9 Hz), 7.17(2H, d, J=8.8 Hz), 7.24(2H, d, J=8.9 Hz)

Example 128



(E0128)

E0128was prepared in a similar manner to that of E0120.

white powder

mp. 110-111℃

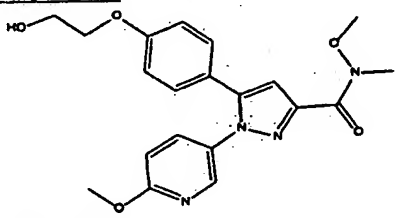
IR (KBr) : 3425, 2979, 2945, 1606, 1570, 1549cm-1

Mass (ESI+) : 397 (M+H)+

200MHz 1H NMR (DMSO-d6, d) :

1.09-1.23(3H, m), 2.98,3.28(3H, s), 3.42-3.73(4H, m), 3.87(3H, s), 3.96-4.02(2H, m), 4.87(1H, t, J=5.3 Hz), 6.82-6.97(4H, m), 7.21(2H, d, J=8.7 Hz), 7.63-7.72(1H, m), 8.14(1H, d, J=2.6 Hz)

Example 129



(E0129)

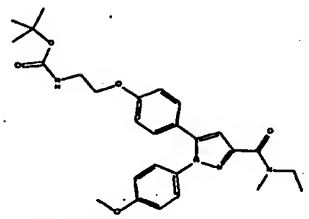
E0129 was prepared in a similar manner to that of E0120.

white powder

Mass (ESI+) : 399 (M+H)+

200MHz 1H NMR (DMSO-d6, d) : 3.37(3H, s), 3.66-3.74(2H, m), 3.77(3H, s), 3.88(3H, s), 3.96-4.02(2H, m), 4.87(1H, t, J=5.5 Hz), 6.88-6.97(4H, m), 7.21(2H, d, J=8.7 Hz), 7.69(1H, dd, J=2.7,8.8 Hz), 8.16(1H, d, J=2.7 Hz)

Example 130



(E0130)

E0130 was prepared in a similar manner to that of E0120.

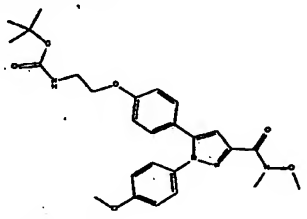
white powder

Mass (ESI+) : 495(M+H)+

400MHz 1H NMR (DMSO-d6, d) :

1. 12,1.18(3H, t, J=7.0 Hz), 1.37(9H, s), 2.97,3.29(3H, s), 3.24-3.28(2H, m), 3.48,3.45(2H, q, J=7.0 Hz), 3.78(3H, s), 3.95(2H, t, J=5.7 Hz), 6.78,6.81(1H, s), 6.91(2H, d, J=8.8 Hz), 6.98(2H, d, J=8.8 Hz), 7.00(1H, overlapping), 7.16(2H, d, J=8.8 Hz), 7.23(2H, d, J=8.9 Hz)
2.

Example 131



(E0131)

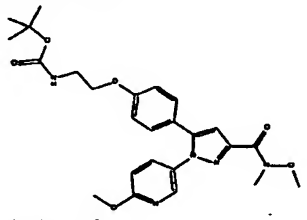
E0131 was prepared in a similar manner to that of E0120.

white powder

Mass (ESI+) : 497 (M+H)+

400MHz 1H NMR (DMSO-d6, d) : 1.37(9H, s), 3.25-3.29(2H, m), 3.37(3H, brs), 3.76(3H, s), 3.78(3H, s), 3.95(2H, t, J=5.7 Hz), 6.88(1H, s), 6.91(2H, d, J=8.8 Hz), 6.99(2H, d, J=8.9 Hz), 6.97-7.00(1H, br), 7.17(2H, d, J=8.8 Hz), 7.24(2H, d, J=8.9 Hz)

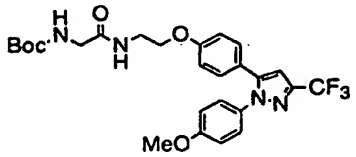
Example 132



(E0132)

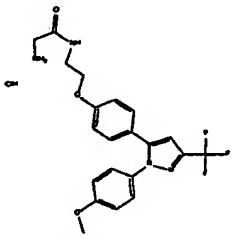
E0132 was prepared in a similar manner to that of E0120.
white powder
Mass (ESI+) : 498 (M+H)+
200MHz 1H NMR (DMSO-d6, d) :
1.37(9H, s), 3.22-3.33(2H, m), 3.37(3H, s), 3.77(3H, s), 3.88(3H, s), 3.93-3.99(2H, m), 6.88-7.05(5H, m), 7.22(2H, d, J=8.6 Hz), 7.69(1H, dd, J=2.7,8.8 Hz), 8.16(1H, d, J=2.7 Hz)

Example 133



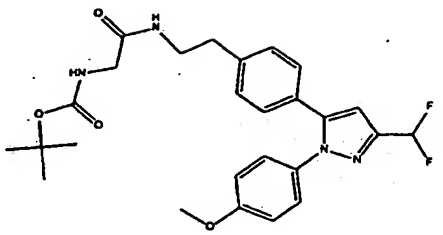
(E0133)
This compound was obtained according to a similar manner to that of E0120 as an oil (371.9 mg, 96%).
NMR(CDCl3); 1.43(9H, s), 3.65-3.73(2H, m), 3.79-3.82(2H, m), 3.82(3H, s), 4.03(2H, t, J=5.2 Hz), 6.67(1H, s), 6.79-6.89(4H, m), 7.14(2H, d, J=8.7 Hz), 7.22(2H, d, J=9.0 Hz).
MS(ESI+); 557.2(M+Na).

Example 134



(E0134)
This compound was obtained according to a similar manner to that of E0194 as a white powder.
NMR(DMSO-d6),3.49-3.63(4H, m), 3.79(3H, s), 4.03(2H, t, J=4.8 Hz), 6.92-7.08(5H, m), 7.21(2H, d, J=8.7 Hz), 7.28(2H, d, J=8.9 Hz).
MS(ESI-), 433.2(M-H).
IR(KBr); 1683cm-1

Example 135

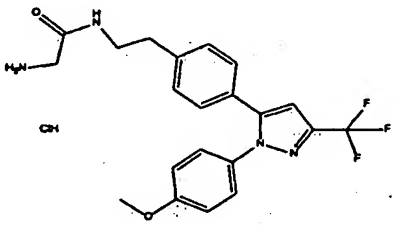


(E0135)

This compound was obtained according to a similar manner to that of E0120.

IR (film): 3320.82, 1706.69, 1668.12, 1515.77, 1249.65, 1168.65, 1031.73 cm-1.

Example 136

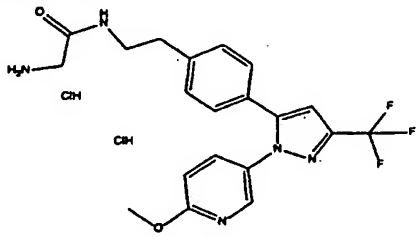


(E0136)

A mixture of E0120 (300mg) and 4NHCl in dioxane (5.8ml) was stirred at room temperature for 1.0 hour. After then, the reaction mixture was evaporated under reduced pressure to give 260mg (99%) of E0136 as an amorphous.

IR(film): 3226.3, 1679.7, 1513.9, 1251.6, 1083.8, 1029.8, 837.0cm-1.

Example 137



(E0137)

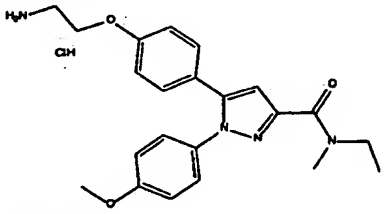
E0137 was prepared in a similar manner to that of E0136.

white powder

IR (KBr) : 3458, 3435, 3404, 3244, 3078, 3026, 1671, 1614, 1579, 1566, 1554, 1500cm-1

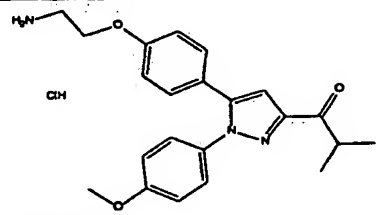
Mass (ESI+) : 420 (M+H)+
200MHz 1H NMR (DMSO-d6, d) : 2.71-2.79(2H, m), 3.30-3.41(2H, m), 3.44-3.54(2H, m), 3.88(3H, s), 6.93(1H, d, J=8.7 Hz), 7.22(1H, s), 7.22-7.33(4H, m), 7.77(1H, dd, J=2.7,8.7 Hz), 8.10(2H, br), 8.19(1H, d, J=2.7 Hz), 8.55(1H, t, J=5.4 Hz)

Example 138



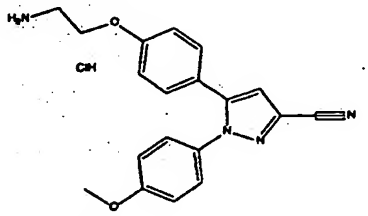
(E0138)
E0138 was prepared in a similar manner to that of E0136.
white powder
mp. 207-209℃
IR (KBr) : 2966, 2933, 2871, 2750, 1606, 1566, 1549, 1512cm-1
Mass (ESI+) : 395 (M+H)+
200MHz 1H NMR (DMSO-d6, d) : 1.08-1.22(3H, m), 2.97,3.29(3H, s), 3.17-3.22(2H, m), 3.40-3.80(2H, m), 3.78(3H, s), 4.14-4.20(2H, m), 6.80,6.83(1H, s), 6.94-7.01(4H, m), 7.18-7.26(4H, m), 8.13(2H, brs)

Example 139



(E0139)
E0139 was prepared in a similar manner to that of E0136.
white powder
mp. 129-142℃
IR (KBr) : 3471, 3437, 2968, 2933, 1674, 1639, 1631, 1612, 1545, 1512cm-1
Mass (ESI+) : 380 (M+H)+
200MHz 1H NMR (DMSO-d6, d) : 1.15(6H, d, J=6.9 Hz), 3.16-3.22(2H, m), 3.68(1H, m), 3.79(3H, s), 4.15-4.20(2H, m), 6.94-7.05(5H, m), 7.22(2H, d, J=8.8 Hz), 7.29(2H, d, J=8.9 Hz), 8.15(2H, brs)

Example 140



(E0140)

E0140 was prepared and in a similar manner to that of E0136.

white powder

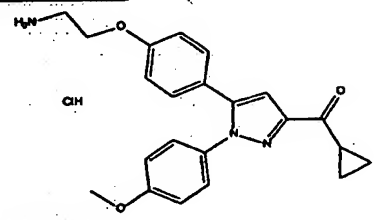
mp. 186-189℃

IR (KBr) : 3209, 3136, 2968, 2873, 1647, 1610, 1547, 1512cm-1

Mass (ESI+) : 335 (M+H)+

200MHz 1H NMR (DMSO-d6, d) : 3.19(2H, t, J=4.9 Hz), 3.79(3H, s), 4.18(2H, t, J=4.9 Hz), 6.96-7.05(4H, m), 7.21(2H, d, J=8.8 Hz), 7.29(2H, d, J=9.0 Hz), 7.32(1H, s), 8.16(2H, brs)

Example 141



(E0141)

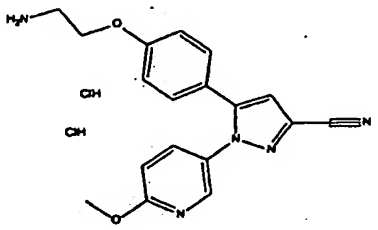
E0141 was prepared in a similar manner to that of E0136.

white powder

Mass (ESI+) : 378 (M+H)+

200MHz 1H NMR (DMSO-d6, d) : 1.04(4H, d, J=6.1 Hz), 3.04(1H, m), 3.14-3.22(2H, m), 3.80(3H, s), 4.15-4.21(2H, m), 6.93-7.05(5H, m), 7.23(2H, d, J=8.6 Hz), 7.31(2H, d, J=8.9 Hz), 8.15(2H, brs)

Example 142



(E0142)

E0142 was prepared in a similar manner to that of E0136.

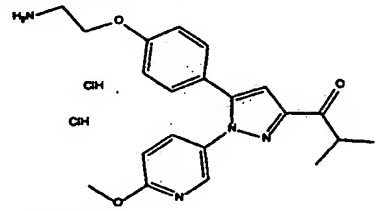
amorphous powder

IR (KBr) : 3433, 3425, 3404, 3043, 3028, 3022, 2962, 1658, 1612cm-1

Mass (ESI+) : 336 (M+H)+

200MHz 1H NMR (DMSO-d6, d) : 3.15-3.24(2H, m), 3.88(3H, s), 4.16-4.22(2H, m), 6.94(1H, d, J=8.8 Hz), 7.01(2H, d, J=8.7 Hz), 7.25(2H, d, J=8.7 Hz), 7.36(1H, s), 7.75(1H, dd, J=2.6,8.8 Hz), 8.10-8.30(2H, br), 8.20(1H, d, J=2.6 Hz)

Example 143



(E0143)

E0143 was prepared in a similar manner to that of E0136.

white powder

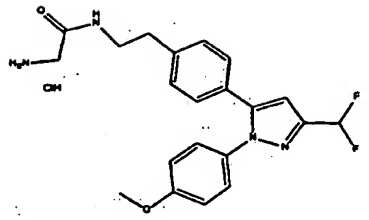
mp. 156-161℃

IR (KBr) : 2970, 1676, 1647, 1612, 1550, 1500cm-1

Mass (ESI+) : 381 (M+H)+

200MHz 1H NMR (DMSO-d6, d) : 1.16(6H, d, J=6.9 Hz), 3.15-3.24(2H, m), 3.68(1H, m), 3.88(3H, s), 4.16-4.22(2H, m), 6.91-7.06(4H, m), 7.26(2H, d, J=8.7 Hz), 7.75(1H, dd, J=2.7,8.9 Hz), 8.18(1H, d, J=2.7 Hz), 8.22(2H, brs)

Example 144

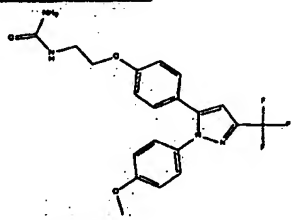


(E0144)

This compound was obtained according to a similar manner to that of E0136.

IR (film): 3220.5, 1679.7, 1513.9, 1461.8, 1251.6, 1081.9, 1029.8, 837.0, 800.3 cm-1.

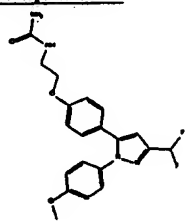
Example 145



(E0145)

To a solution of E0172 (75.2 mg) in dichloromethane (1 ml) was added triethylamine (30.4 ml) and trimethylsilyl isocyanate (36.9 ml) at 0℃. After stirring for 5 hours, the mixture was quenched with water and extracted with dichloromethane. The combined organic layers were washed with brine, dried over magnesium sulfate, and evaporated under reduced pressure to give oil, which was purified with preparative TLC (1 mm, ethyl acetate) to give oil. The oil was crystallized from a mixture of isopropyl ether, ethyl acetate, and hexane to give E0145 (FR270355) as a white solid (39.1 mg, 51.2%).
NMR(DMSO-d6); 3.27-3.32(2H, m), 3.79(3H, s), 3.94(2H, t, J=5.6 Hz), 5.52(2H, brs, NH2), 6.15(1H, t, J=5.6 Hz, NH), 6.94(2H, d, J=8.8 Hz), 7.00(2H, d, J=8.9 Hz), 7.07(1H, s), 7.20(2H, d, J=8.8 Hz), 7.28(2H, d, J=8.9 Hz).
MS(ESI+); 443.2(M+Na).
IR(KBr), 1685.5, 1656.6cm-1.

Example 146



(E0146)

E0146 was prepared from E0194 in a similar manner to that of E0145.

white powder

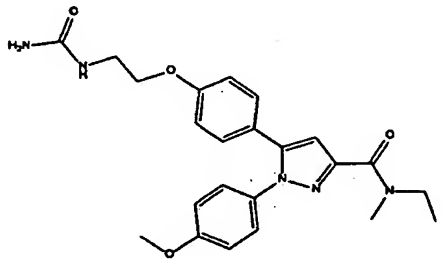
mp. 139-140℃

IR (KBr) : 3458, 3342, 1691, 1647, 1604, 1572, 1529cm-1

Mass (ESI+) : 404 (M+H)+

200MHz 1H NMR (DMSO-d6, d) : 3.28-3.36(2H, m), 3.87(3H, s), 3.92-3.98(2H, m), 5.52(2H, brs), 6.15(1H, t, J=5.5 Hz), 6.88-6.98(4H, m), 7.10(1H, t, J=54.4 Hz), 7.22(2H, d, J=8.7 Hz), 7.69(1H, dd, J=2.7,8.8 Hz), 8.14(1H, d, J=2.7 Hz)

Example 147



(E0147)

E0147 was prepared in a similar manner to that of E0145.

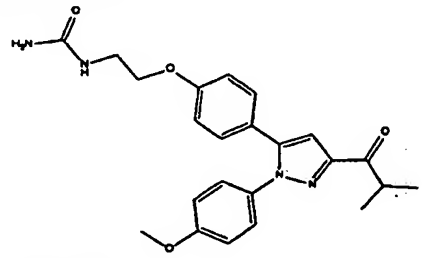
white powdermp. 108-113℃

IR (KBr) : 3492, 3435, 3425, 3359, 3298, 1647, 1614, 1564, 1549, 1512cm-1

Mass (ESI+) : 438 (M+H)+

200MHz 1H NMR (DMSO-d6, d) : 1.08-1.22(3H, m), 2.97,3.29(3H, s), 3.20-3.85(4H, m), 3.78(3H, s), 3.94(2H, t, J=5.5 Hz), 5.53(2H, s), 6.15(1H, t, J=5.6 Hz), 6.79,6.81(1H, s), 6.92(2H, d, J=8.8 Hz), 6.99(2H, d, J=8.9 Hz), 7.17(2H, d, J=8.8 Hz), 7.23(2H, d, J=8.9 Hz)

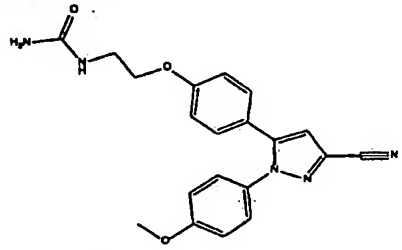
Example 148



(E0148)

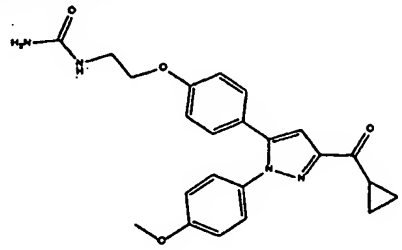
E0148 was prepared from E0139 in a similar manner to that of E0145.
white powder
mp. 144-145℃
IR (KBr) : 3435, 3369, 3176, 2970, 1674, 1612, 1547, 1514cm-1
Mass (ESI+) : 423 (M+H)+
200MHz 1H NMR (DMSO-d6, d) : 1.15(6H, d, J=6.9 Hz), 3.27-3.36(2H, m), 3.68(1H, m), 3.79(3H, s), 3.90-3.97(2H, m), 5.53(2H, s), 6.15(1H, t, J=5.6 Hz), 6.92(2H, d, J=8.7 Hz), 6.98(1H, s), 7.00(2H, d, J=8.9 Hz), 7.18(2H, d, J=8.7 Hz), 7.28(2H, d, J=8.9 Hz)

Example 149



(E0149)
E0149 was prepared from E0140 in a similar manner to that of E0145.
white powder
mp. 187-190℃
IR (KBr) : 3379, 3201, 1649, 1614, 1579, 1527, 1506cm-1
Mass (ESI+) : 378 (M+H)+
200MHz 1H NMR (DMSO-d6, d) : 3.27-3.34(2H, m), 3.79(3H, s), 3.94(2H, t, J=5.5 Hz), 5.52(2H, brs), 6.14(1H, t, J=5.6 Hz), 6.94(2H, d, J=8.8 Hz), 7.00(2H, d, J=9.0 Hz), 7.17(2H, d, J=8.8 Hz), 7.24-7.31(3H, m)

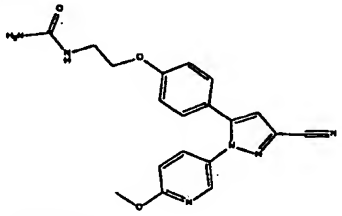
Example 150



(E0150)
E0150 was prepared in a similar manner to that of E0145.
white powder

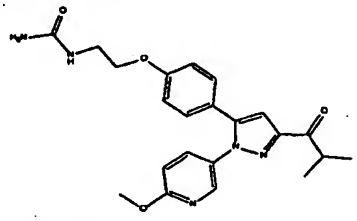
mp. 136-137℃
IR (KBr) : 3433, 3342, 3221, 1658, 1612, 1581, 1549, 1512cm-1
Mass (ESI+) : 421 (M+H)+
200MHz 1H NMR (DMSO-d6, d) : 1.04(4H, d, J=6.2 Hz), 3.03(1H, m), 3.27-3.36(2H, m), 3.80(3H, s), 3.90-3.97(2H, m), 5.52(2H, s), 6.14(1H, t, J=5.6 Hz), 6.93(2H, d, J=8.8 Hz), 6.97(1H, s), 7.01(2H, d, J=8.9 Hz), 7.19(2H, d, J=8.8 Hz), 7.30(2H, d, J=8.9 Hz)

Example 151



(E0151)
E0151 was prepared in a similar manner to that of E0145.
white powder
mp. 173-176℃
IR (KBr) : 3473, 3334, 1630, 1624, 1601, 1583cm-1
Mass (ESI+) : 379 (M+H)+
200MHz 1H NMR (DMSO-d6, d) : 3.27-3.36(2H, m), 3.88(3H, s), 3.92-3.98(2H, m), 5.52(2H, s), 6.14(1H, t, J=5.7 Hz), 6.93(1H, d, J=8.8 Hz), 6.97(2H, d, J=8.8 Hz), 7.21(2H, d, J=8.8 Hz), 7.35(1H, s), 7.73(1H, dd, J=2.7,8.8 Hz), 8.20(1H, d, J=2.7 Hz)

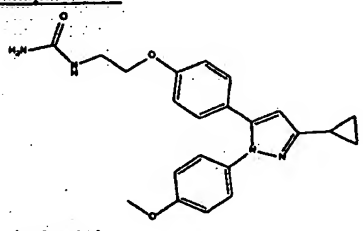
Example 152



(E0152)
E0152 was prepared in a similar manner to that of E0145.
white powder
mp. 145-147℃
IR (KBr) : 3367, 3174, 2972, 1689, 1674, 1610, 1566, 1502cm-1
Mass (ESI+) : 424 (M+H)+
200MHz 1H NMR (DMSO-d6, d) : 1.16(6H, d, J=6.9 Hz), 3.28-3.37(2H, m), 3.68(1H,

m), 3.88(3H, s), 3.92-3.98(2H, m), 5.52(2H, s), 6.15(1H, t, J=5.6 Hz), 6.93(1H, d, J=8.7 Hz), 6.95(2H, d, J=8.8 Hz), 7.02(1H, s), 7.22(2H, d, J=8.8 Hz), 7.73(1H, dd, J=2.7,8.7 Hz), 8.19(1H, d, J=2.7 Hz)]

Example 153



(E0153)

E0153 was prepared in a similar manner to that of E0145.

white powder

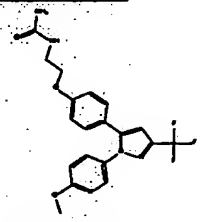
mp. 150.8-151.0℃

IR (KBr) : 3496, 3361, 3294, 1705, 1674, 1647, 1603, 1581, 1568, 1554, 1516cm-1

Mass (ESI+) : 393 (M+H)+

200MHz 1H NMR (DMSO-d6, d) : 0.71-0.77(2H, m), 0.85-0.92(2H, m), 1.92(1H, m), 3.27-3.37(2H, m), 3.76(3H, s), 3.92(2H, t, J=5.5 Hz), 5.51(2H, s), 6.14(1H, t, J=5.5 Hz), 6.24(1H, s), 6.86-6.96(4H, m), 7.07-7.15(4H, m)

Example 154



(E0154)

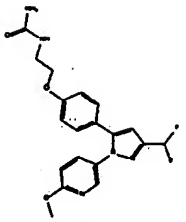
This compound was obtained according to a similar manner to that of E0145 as an amorphous.

NMR(CDCl3), 3.56-3.64(2H, m), 3.94(3H, s), 4.04(2H, t, J=4.9 Hz), 4.50(2H, brs, NH2), 6.69(1H, s), 6.76(1H, d, J=8.8 Hz), 6.84(2H, d, J=8.8 Hz), 7.12(2H, d, J=8.8 Hz), 7.58(1H, dd, J=8.8, 2.8 Hz), 8.05(1H, d, J=2.8 Hz).

MS(ESI+), 444.1 (M+Na)+. IR(KBr); 1650.8, 1608.3cm-1.

LCMS(ESI+), 422.27(MH+).

Example 155



(E0155)

This compound was obtained according to a similar manner to that of E0145 as a white powder.

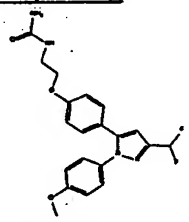
NMR(CDCl3), 3.55-3.63(2H, m), 3.93(3H, s), 4.04(2H, t, J=5.1 Hz), 4.55(2H, brs, NH2), 5.23(1H, brt, J=5.4 Hz, NH), 6.67(1H, s), 6.75(1H, t, J=55 Hz), 6.75(1H, d, J=8.4 Hz), 6.88(2H, d, J=8.8 Hz), 7.13(2H, d, J=8.8 Hz), 7.56(1H, d, J=8.4, 2.9 Hz), 8.04(1H, d, J=2.9 Hz).

LCMS(ESI+), 404.39(MH+).

IR(KBr) 1649cm-1

MP, 141.5 - 142.1℃.

Example 156



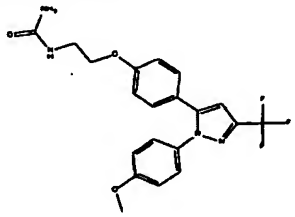
(E0156)

This compound was obtained according to a similar manner to that of E0145 as a powder.

NMR(CDCl3), 3.56-3.64(2H, m), 3.82(3H, s), 4.03(2H, t, J=5.0 Hz), 4.42(2H, brs), 6.65(1H, s), 6.76(1H, t, J=55 Hz), 6.79-6.89(4H, m), 7.14(2H, d, J=8.7 Hz), 7.20(2H, d, J=9.0 Hz).

MS(ESI+), 425(M+Na)+.

Example 157

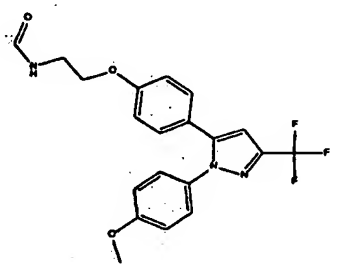


(E0157)

To a solution of E0172 (15.3 g) in ethanol (75 ml) and hydrogen chloride aqueous solution (1N, 220 ml) was added dropwise a solution of sodium cyanate (14.4 g) in water (300 ml) at 45℃ over 5 minutes. After stirring at 45℃ for 4 hours, the mixture was quenched with saturated sodium hydrogen carbonate aqueous solution and extracted with ethyl acetate. The combined organic layers were washed with brine, dried over magnesium sulfate, and evaporated to give powder. The powder was crystallized from ethyl acetate and hexane at room temperature ~ 70℃ to give E0157 as a powder (12.628 g, 81.2%).

The physical data of this compound was identical to previously obtained authentic sample.

Example 158



(E0158)

To a solution of E0172 (200 mg) in methanol (1 ml) was added sodium methoxide methanol solution (5.2M, 0.1 ml) at room temperature. After stirring for 20 minutes, the mixture was evaporated to give residue. To the residue was added tetrahydrofuran, and the mixture was filtered and evaporated to give oil.

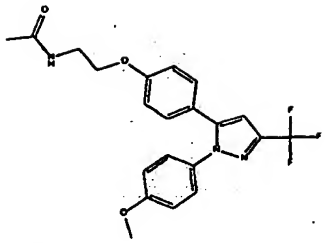
The oil was dissolved in ethyl formate (2 ml) and stirred at room temperature overnight. The mixture was evaporated and purified with preparative TLC(1 mm, 50% ethyl acetate/hexane) to give oil, which was crystallized from isopropyl ether, ethyl acetate, and hexane to give E0158 as a white powder (162.8 mg, 83%).

NMR(CDCl3), 3.68-3.76(2H, m), 3.82(3H, s), 4.06(2H, t, J=5.0 Hz), 6.68(1H, s), 6.80-6.89(4H, m), 7.14(2H, d, J=8.7 Hz), 7.22(2H, d, J=9.0 Hz), 8.22(1H, s).

MS(ESI+), 428.2(M+Na).

IR(KBr), 1660.4, 1614.1cm-1.

Example 159



(E0159)

To a solution of E0172 (800 mg) and triethylamine (0.7 ml) in dichloromethane (9 ml) was added dropwise acetyl chloride (0.18 ml) at 0℃. After stirring at room temperature for 1 hour,

the mixture was quenched with saturated sodium hydrogen carbonate aqueous solution and extracted with ethyl acetate (x3). The combined organic layers were washed with hydrogen chloride aqueous solution (1N), water, and brine, dried over magnesium sulfate, and evaporated to give oil, which was purified with column chromatography (SiO_2 100 ml, eluted with 50% ethyl acetate/hexane) to give oil. The oil was crystallized from a mixture of ethyl acetate and hexane at 50℃ to give E0159 as a solid (768.6 mg, 94.8%).

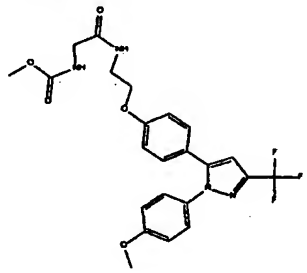
NMR(CDCl3). 2.01(3H, s), 3.62-3.70(2H, m), 3.82(3H, s), 4.03(2H, t, J=5.0 Hz), 6.67(1H, s), 6.80-6.91(4H, m), 7.14(2H, d, J=8.7 Hz), 7.22(2H, d, J=9.0 Hz).

MP; 109.8 - 110.2℃

IR(KBr), 1649cm-1.

MS(ESI+).442.1(M+Na).

Example 160



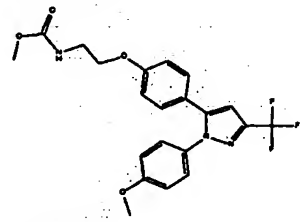
(E0160)

This compound was obtained according to a similar manner to that of E0159 as an oil.

NMR(CDCl3), 3.69(3H, s), 3.65-3.73(2H, m), 3.82(3H, s), 3.86(2H, d, J=5.9 Hz), 4.04(2H, t, J=5.1 Hz), 6.67(1H, s), 6.80-6.89(4H, m), 7.14(2H, d, J=8.5 Hz), 7.22(2H, d, J=8.9 Hz),

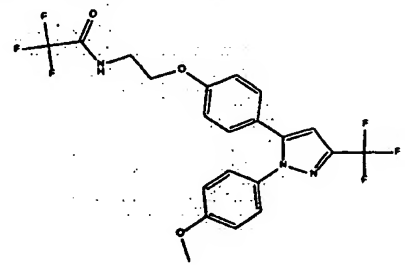
MS(ESI+).515.2(M+Na).
IR(KBr, 20727-10), 1722.1, 1710.6, 1673.9cm-1.

Example 161 (



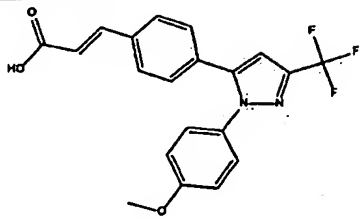
(E0161)
This compound was obtained according to a similar manner to that of E0159 (S0203793) as an oil (82 mg, 78%).
MS(ESI+).458.2(M+Na).
IR(Neat), 1699cm-1.
NMR(CDCl3); 3.54-3.62(2H, m), 3.69(3H, s), 3.82(3H, s), 4.02(2H, t), 6.67(1H, s), 6.80-6.89(4H, m), 7.13(2H, d, J=8.9 Hz), 7.22(2H, d, J=9.0 Hz).

Example 162



(E0162)
To a solution of E0180 (97.5 mg) and pyridine (0.14 ml) in dichloromethane (1 ml) was added trifluoroacetic anhydride (60.6 ml) at 0℃. After stirring at room temperature overnight, the mixture was quenched with saturated sodium hydrogen carbonate aqueous solution (0.5 ml), filtered with chemelute1001 (Varian), and purified with preparative TLC(1 mm, 50% ethyl acetate/hexane) to give E0162 as a solid (92.5 mg, 76%).
MS(ESI+), 496.1(M+Na).
IR(KBr), 1705cm-1.
NMR(CDCl3),3.75-3.87(2H, m), 3.82(3H, s), 4.10(4.8H, t), 6.68(1H, s), 6.83(2H, d, J=8.8 Hz), 6.88(2H, d, J=8.9 Hz), 7.16(2H, d, J=8.8 Hz), 7.22(2H, d, J=8.9 Hz).

Example 163

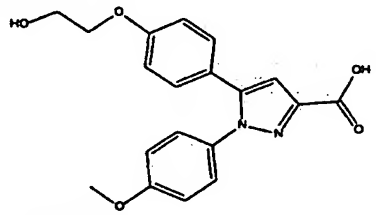


(E0163)

To a solution of E0238 (400mg) in THF (5ml) was added dropwise 1N NaOH (2.5ml) at room temperature. The mixture was stirred overnight, and then quenched with 1N HCl and CHCl3. The organic layer was separated and water layer was extracted twice with CHCl3. The combined organic layer was washed with water and brine, dried over Na2SO4, and evaporated under reduced pressure. The residue was washed with IPE to give 273mg (70.7%) of E0163.

IR (film): 2971.8, 1683.6, 1629.6, 1515.8, 1315.2, 1230.4, 1159.0, 1132.0, 977.7, 835.0cm-1.

Example 164



(E0164)

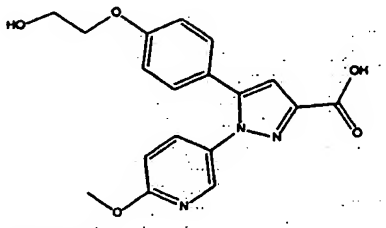
E0164 was prepared in a similar manner to that of E0163.

white powder

Mass (ESI+) : 355 (M+H)+

200MHz 1H NMR (DMSO-d6, d) : 3.63-3.78(2H, m), 3.79(3H, s), 3.95-4.00(2H, m), 4.86(1H, brs), 6.91(2H, d, J=8.7 Hz), 6.95(1H, s), 6.99(2H, d, J=8.9 Hz), 7.16(2H, d, J=8.7 Hz), 7.24(2H, d, J=8.9 Hz), 12.88(1H, brs)

Example 165



(E0165)

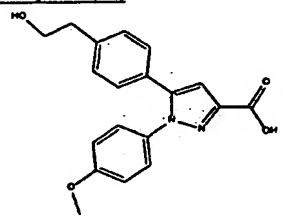
E0165 was prepared in a similar manner to that of E0163.

white powder

Mass (ESI+) : 356 (M+H)+

200MHz 1H NMR (DMSO-d6, d) : 3.69-3.79(2H, m), 3.88(3H, s), 3.96-4.02(2H, m), 4.87(1H, br), 6.89-7.00(4H, m), 7.20(2H, d, J=8.8 Hz), 7.70(1H, dd, J=2.6,8.8 Hz), 8.14(1H, d, J=2.6 Hz), 12.97(1H, br)

Example 166



(E0166)

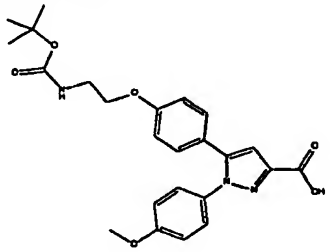
E0166 was prepared from E0005 in a similar manner to that of E0163.

white powder

Mass (ESI+) : 339(M+H)+

200MHz 1H NMR (DMSO-d6, d) : 2.70(2H, t, J=6.9 Hz), 3.59(2H, t, J=6.9 Hz), 3.79(3H, s), 4.64(1H, brs), 6.96-7.03(3H, m), 7.12-7.28(6H, m), 12.90(1H, br)

Example 167



(E0167)

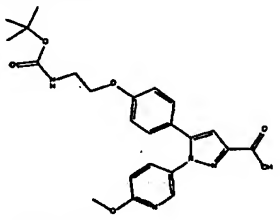
E0167 was prepared in a similar manner to that of E0163.

white powder

Mass (ESI+) : 454 (M+H)+

200MHz 1H NMR (DMSO-d6, d) : 1.37(9H, s), 3.22-3.32(2H, m), 3.79(3H, s), 3.91-3.98(2H, m), 6.90(2H, d, J=8.7 Hz), 6.90-7.03(1H, overlapping), 6.95(1H, s), 6.99(2H, d, J=8.9 Hz), 7.16(2H, d, J=8.7 Hz), 7.24(2H, d, J=8.9 Hz)

Example 168



(E0168)

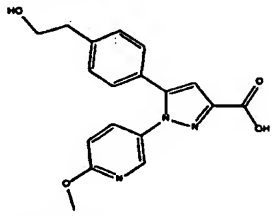
E0168 was prepared in a similar manner to that of E0163.

amorphous powder

Mass (ESI+) : 455 (M+H)+

200MHz 1H NMR (DMSO-d6, d) : 1.37(9H, s), 3.22-3.32(2H, m), 3.88(3H, s), 3.93-3.98(2H, m), 6.89-7.05(5H, m), 7.20(2H, d, J=8.7 Hz), 7.70(1H, dd, J=2.7,8.8 Hz), 8.14(1H, d, J=2.7 Hz), 12.98(1H, br)

Example 169



(E0169)

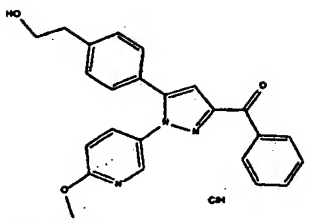
E0169 was prepared from E0006 in a similar manner to that of E0163.

white powder

Mass (ESI+) : 340 (M+H)+

200MHz 1H NMR (DMSO-d6, d) : 2.71(2H, t, J=6.9 Hz), 3.56-3.64(2H, m), 3.88(3H, s), 4.64(1H, br), 6.92(1H, d, J=8.8 Hz), 7.03(1H, s), 7.16-7.28(4H, m), 7.72(1H, dd, J=8.8,2.7 Hz), 8.15(1H, d, J=2.7 Hz), 12.94(1H, br)

Example 170



(E0170)

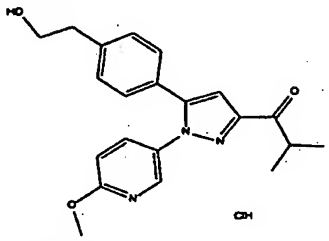
4M HCl/AcOEt 0.4ml was added to a solution of E0289 (73mg) in AcOEt 1ml. The mixture was concentrated and dried in vacuo to give E0170 68.4mg as an amorphous powder.

IR (neat) : 3440, 2960, 1739, 1707, 1691, 1674, 1647, 1624, 1614, 1566, 1549, 1533, 1500cm-1

Mass (ESI+) : 400 (M+H)+

200MHz 1H NMR (DMSO-d6, d) : 2.73(2H, t, J=6.9 Hz), 3.62(2H, t, J=6.9 Hz), 3.89(3H, s), 6.94(1H, d, J=8.8 Hz), 7.19-7.32(5H, m), 7.52-7.70(3H, m), 7.80(1H, dd, J=8.8,2.7 Hz), 8.22-8.28(3H, m)

Example 171



(E0171)

E0171 was prepared in a similar manner to that of E0170.

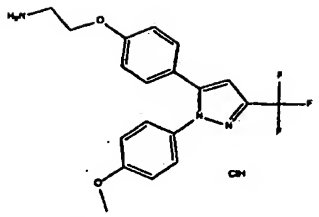
oil

IR (neat) : 3435, 2966, 2935, 1678, 1662, 1649, 1612, 1581, 1566, 1547, 1533, 1500cm-1

Mass (ESI+) : 366 (M+H)+

200MHz 1H NMR (DMSO-d6, d) : 1.16(6H, d, J=6.9 Hz), 2.72(2H, t, J=6.9 Hz), 3.54-3.75(3H, m), 3.89(3H, s), 6.93(1H, d, J=8.8 Hz), 7.05(1H, s), 7.13-7.35(4H, m), 7.76(1H, dd, J=2.7,8.8 Hz), 8.19(1H, d, J=2.7 Hz)

Example 172



(E0172)

To a solution of E0180 (765 mg) in ethyl acetate (1.9 ml) was added a solution of hydrogen chloride in ethyl acetate (4N, 0.56 ml). The mixture was evaporated to give oil, which was crystallized from diisopropyl ether and ethyl acetate at 65℃ to give E0172 as a solid (766.8 mg, 91.4%).

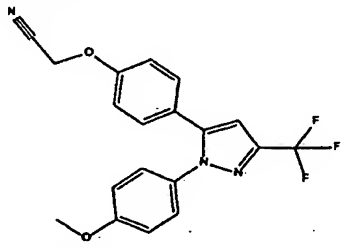
NMR(CDCl3), 3.30(2H, t, J=5.0 Hz), 3.79(3H, s), 4.18(2H, t, J=5.0 Hz), 6.62(1H, s), 6.83-6.88(4H, m), 7.10(2H, d, J=8.8 Hz), 7.18(2H, d, J=8.8 Hz).

NMR(DMSO-d6), 3.19(2H, brs), 3.79(3H, s), 4.18(2H, t, J=5.0 Hz), 6.96-7.01(4H, m), 7.08(1H, s), 7.23-7.29(4H, m).

MS(ESI+), 378.3(MH+, free).

IR(KBr, 20727-2), 1612.2, 1513.9cm-1.

Example 173



(E0173)

A mixture of P0011 (30 g), chloroacetonitrile (8.52 ml), potassium iodide (4.47 g), and potassium carbonate (14.9 g) in acetone (150 ml) was stirring under reflux at 80℃ for 2.5 hours.

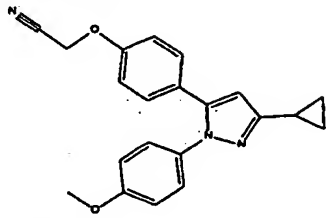
After cooling to room temperature, the mixture was quenched with water (600 ml) and extracted with ethyl acetate (300 ml x 2, 150 ml). The combined organic layers were washed with brine (300 ml), dried over magnesium sulfate, and evaporated to give solid (36.34 g).

The solid was recrysallized from diisopropyl ether (60 ml) and hexane (200 ml) at room temperature to give E0173 as a powder (31.5 g, 94%).

NMR(CDCl3), 3.83(3H, s), 4.78(2H, s), 6.70(1H, s), 6.86-6.97(4H, m), 7.18-7.24(4H, m).

IR(KBr), 2051.9cm-1.

Example 174



(E0174)

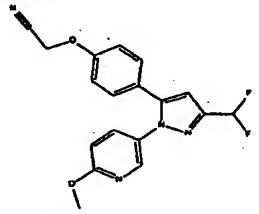
FR277063 was prepared from P0034 in a similar manner to that of E0173.

white powder

Mass (ESI+) : 346(M+H)+

200MHz 1H NMR (DMSO-d6, d) : 0.69-0.77(2H, m), 0.86-0.96(2H, m), 1.92(1H, m), 3.76(3H, s), 5.16(2H, s), 6.30(1H, s), 6.93(2H, d, J=9.0 Hz), 7.02(2H, d, J=8.8 Hz), 7.10-7.21(4H, m)

Example 175



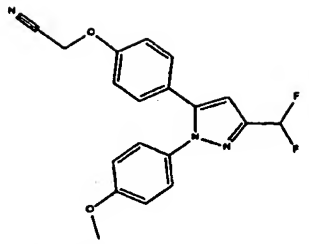
(E0175)

This compound was obtained according to a similar manner to that of E0173 as a powder.

NMR(CDCl3), 3.95(3H, s), 4.78(2H, s), 6.71(1H, s), 6.76(1H, t, J=55 Hz), 6.76(1H, d, J=8.4 Hz), 6.96(2H, d, J=8.9 Hz), 7.23(2H, d, J=8.9 Hz), 7.53(1H, dd, J=8.4, 2.6 Hz), 8.08(1H, d, J=2.6 Hz).

MS(ESI+),379(M+Na).

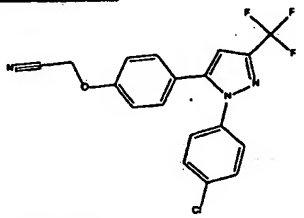
Example 176



(E0176)

This compound was obtained according to a similar manner to that of E0173.

Example 177

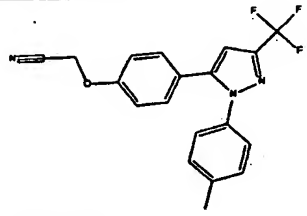


(E0177)

This compound was obtained according to a similar manner to that of E0173.

IR (film): 1612.2, 1482.9, 1234.2, 1162.8, 1132.0, 1095.3, 973.8, 835.0 cm-1.

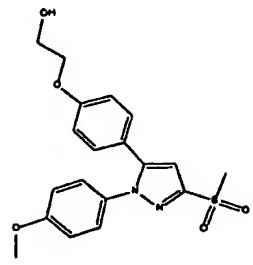
Example 178



(E0178)

This compound was obtained according to a similar manner to that of E0173.

Example 179



(E0179)

This compound was obtained according to a similar manner to that of E0173.

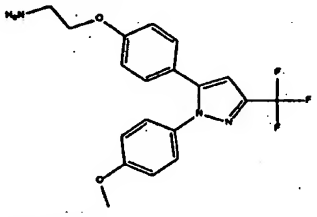
mp.96-99℃

Mass;389(M+1)

NMR(CDCl3,δ);

1.98(1H, t, J=6.1 Hz), 3.29(3H, s), 3.83(3H, s), 3.93-4.01(2H, m), 4.06-4.11(2H, m), 6.86(2H, d, J=8.8 Hz), 6.88(2H, d, J=9.0 Hz), 6.93(1H, s), 7.14(2H, d, J=8.8 Hz), 7.23(2H, d, J=9.0 Hz)

Example 180



(E0180)

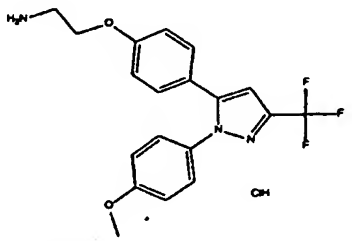
To a suspension of lithium aluminum hydride (250 mg) in ether (14 ml) was added E0173 (1.38 g) in ether (5 ml) and tetrahydrofuran (1 ml) under ice-bath. The mixture was stirred at room temperature for 1 hour. Lithium aluminum hydride (50 mg) was added to the mixture under ice-bath., and then the mixture was stirred at room temperature for 1 hour.

The mixture was quenched with water (0.3 ml), sodium hydroxide aqueous solution (15%, 0.3 ml), and water (0.9 ml), and then stirred at room temperature for 30 minutes. Magnesium sulfate and celite was added to the mixture, then the suspension was filtered and washed with ether. The filtrate was evaporated to give 1.307 g of oil. The oil purified with column chromatography (SiO_2, 100 ml, eluted with 20% methanol / chloroform (500 ml)) to give E0180 as an oil (1.156 g, 82.9%).

NMR(CDCl3), 3.09(2H, t, J=5.1 Hz), 3.82(3H, s), 3.99(2H, t, J=5.1 Hz), 6.67(1H, s), 6.82-6.89(4H, m), 7.14(2H, d, J=8.9 Hz), 7.23(2H, d, J=9.0 Hz).

MS(ESI+), 378(MH+).

Example 181

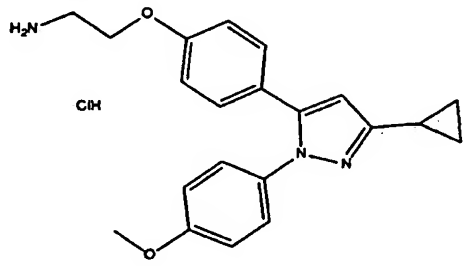


(E0181)

To a solution of E0173 (27.43 g) in tetrahydrofuran (270 ml) was added borane methylsulfide complex (10M, 15 ml) at room temperature. The mixture was stirred at room temperature overnight. Then borane methylsulfide complex (7.5 ml) was added to the mixture. After stirring at room temperature overnight, the mixture was quenched with methanol (100 ml) and evaporated under reduced pressure to give oil. The oil was dissolved in a mixture of tetrahydrofuran (150 ml) and hydrochloric acid (6N, 100 ml), and then stirred at 40 ~ 50℃ for 1 hour. To the mixture was added dropwise aqueous sodium hydroxide solution (30%, 80 ml), and then sodium hydrogen carbonate, and sodium chloride. The mixture was extracted with ethyl acetate (x4). The organic layer was evaporated to give oil (31.86 g), which was purified with column chromatography (SiO_2, 1 L, eluted with 20% methanol/dichloromethane and concentrated ammonia/methanol/chloroform (0.025:1:4)) to give oil.

A solution of hydrogen chloride in ethyl acetate (4N, 22 ml) was added to the solution of the oil in ethyl acetate (50 ml), and the mixture was evaporated to give E0181 as an amorphous (22.87 g, 69.4%).

Example 182



(E0182)

E0182 was prepared in a similar manner to that of E0181.

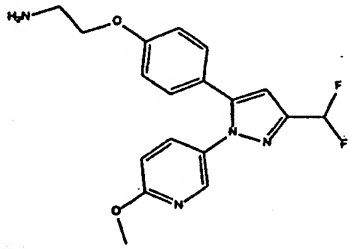
white powder

mp. 229-231℃

IR (KBr) : 3084, 2960, 2885, 2800, 2731, 2563, 2519, 2482, 1606, 1576, 1516cm-1

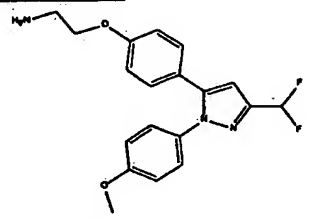
Mass (ESI+) : 350 (M+H)+
200MHz 1H NMR (DMSO-d6, d) : 0.69-0.77(2H, m), 0.84-0.96(2H, m), 1.93(1H, m), 3.14-3.22(2H, m), 3.76(3H, s), 4.14-4.20(2H, m), 6.26(1H, s), 6.94(4H, d, J=8.8 Hz), 7.14(4H, d, J=8.8 Hz), 8.21(2H, brs)

Example 183



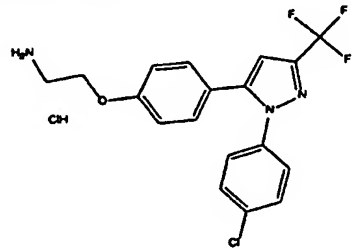
(E0183)
This compound was obtained according to a similar manner to that of E0181 without formation of hydrogen chloride salt (oil).
NMR(CDCl3), 3.09(2H, t, J=5.2 Hz), 3.94(3H, s), 3.99(2H, t, J=5.2 Hz), 6.77(1H, t, J=54.9 Hz), 6.67(1H, s), 6.74(2H, d, J=7.5 Hz), 6.87(2H, d, J=8.9 Hz), 7.15(2H, d, J=8.7 Hz), 7.55(1H, dd, J=8.9, 2.8 Hz), 8.09(1H, d, J=2.8 Hz).
MS(ESI+), 361(MH+).

Example 184



(E0184)
This compound was obtained according to a similar manner to that of E0181.

Example 185

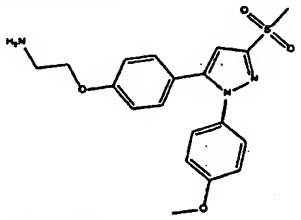


(E0185)

This compound was obtained according to a similar manner to that of E0181.

IR (film): 3423.0, 1612.2, 1469.5, 1240.0, 1164.8, 1132.0, 1095.4, 975.8, 836.9 cm-1.

Example 186



(E0186)

This compound was obtained according to a similar manner to that of E0181.

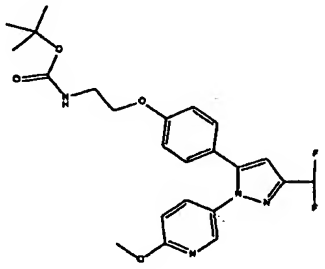
mp.104-106℃

Mass;388(M+1)

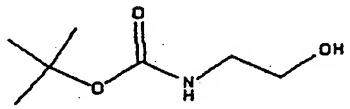
IR(KBr);1310cm-1

NMR(CDCl3,δ);3.09(2H, t, J=5.1 Hz), 3.29(3H, s), 3.83(3H, s), 3.99(2H, t, J=5.1 Hz), 6.83(2H, d, J=8.8 Hz), 6.88(2H, d, J=8.9 Hz), 6.93(1H, s), 7.13(2H, d, J=8.8 Hz), 7.24(2H, d, J=8.9 Hz),

Example 187



(E0187)



(P0015-1)

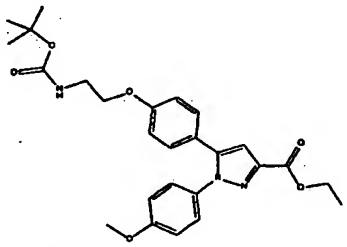
Diethylazodicarboxylate 82.3mg was added to a solution of P0015 (100mg), P0015-1 (152mg), and triphenylphosphine 124mg in THF 2ml. After stirring at ambient temperature for 5 hours, Thereaction mixture was concentrated in vacuo. The residue was purified by silica gel column chromatography eluted with AcOEt / CHCl3 = 5%. viscous oil to give E0187.

Mass (ESI+): 461 (M+H)+

200MHz 1H NMR (DMSO-d6, d) : 1.37(9H, s), 3.22-3.33(2H, m), 3.87(3H, s), 3.93-3.99(2H, m), 6.88-7.04(5H, m), 7.10(1H, t, J=54.4 Hz), 7.21(2H, d, J=8.7 Hz),

7.69(1H, dd, J=2.7,8.8 Hz), 8.14(1H, d, J=2.7 Hz)

Example 188



(E0188)

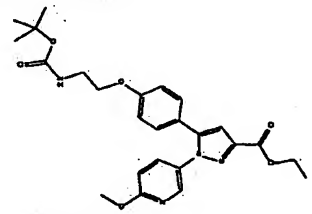
E0188 was prepared from P0020 in a similar manner to that of E0187.

white powder

Mass (ESI+) : 482 (M+H)+

200MHz 1H NMR (DMSO-d6, d) : 1.31(3H, t, J=7.1 Hz), 1.37(9H, s), 3.22-3.32(2H, m), 3.79(3H, s), 3.91-3.98(2H, m), 4.32(2H, q, J=7.1 Hz), 6.90(2H, d, J=8.7 Hz),6.95-7.06(1H, overlapping), 6.99(2H, d, J=8.9 Hz), 7.01(1H, s), 7.17(2H, d, J=8.7 Hz), 7.25(2H, d, J=8.9 Hz)

Example 189



(E0189)

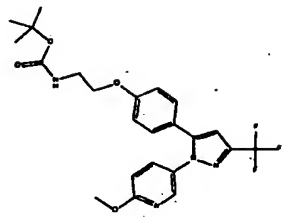
E0189 was prepared in a similar manner to that of E0187.

white powder

Mass (ESI+) : 483 (M+H)+

200MHz 1H NMR (DMSO-d6, d) : 1.31(3H, t, J=7.1 Hz), 1.37(9H, s), 3.22-3.33(2H, m), 3.88(3H, s), 3.96(2H, t, J=5.7 Hz), 4.33(2H, q, J=7.1 Hz), 6.89-7.05(1H, overlapping), 6.92(1H, d, J=8.9 Hz), 6.93(2H, d, J=8.7 Hz), 7.05(1H, s), 7.21(2H, d, J=8.7 Hz), 7.72(1H, dd, J=2.7,8.9 Hz), 8.15(1H, d, J=2.7 Hz)

Example 190



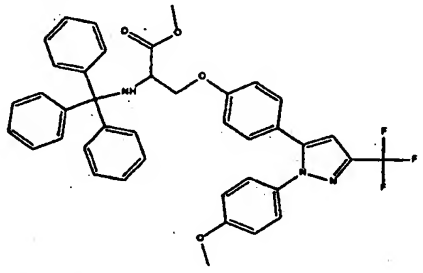
(E0190)

This compound was obtained according to a similar manner to that of E0187 as an oil.

NMR(CDCl3), 1.45(9H, s), 3.50-3.58(2H, m), 3.94(3H, s), 4.02(2H, t, J=5.1 Hz), 6.70(1H, s), 6.75(1H, d, J=8.4 Hz), 6.85(2H, d, J=8.9 Hz), 7.15(2H, d, J=8.9 Hz), 7.56(1H, dd, J=8.4, 2.9 Hz), 8.08(1H, d, J=2.9 Hz).

MS(ESI+), 501.2(M+Na).

Example 191



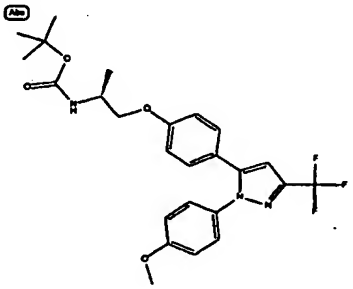
(E0191)

This compound was obtained according to a similar manner to that of E0187 as a powder.

NMR(CDCl3), 2.89(1H, d, J=10.4 Hz, NH), 3.23(3H, s), 3.67-3.78(1H, m), 3.81(3H, s), 3.99(1H, dd, J=9.2, 6.4 Hz), 4.22(1H, dd, J=9.2, 5.0 Hz), 6.67(1H, s), 6.81(2H, d, J=8.9 Hz), 6.86(2H, d, J=6.0 Hz), 7.10-7.29(13H, m), 7.49-7.54(6H, m).

MS(ESI+), 678.4(MH+).

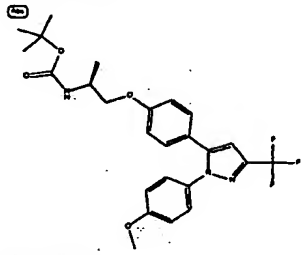
Example 192



(E0192)

This compound was obtained according to a similar manner to that of E0187 as an oil.
NMR(CDCl3), 1.28(3H, d, J=6.6 Hz), 1.45(9H, s), 3.82(3H, s), 3.92(2H, d, J=4.1 Hz), 3.90-4.14(1H, m), 6.67(1H, s), 6.84(2H, d, J=8.9 Hz), 6.86(2H, d, J=9.0 Hz), 7.13(2H, d, J=8.9 Hz), 7.23(2H, d, J=9.0 Hz).
MS(ESI+), 514.2(M+Na).

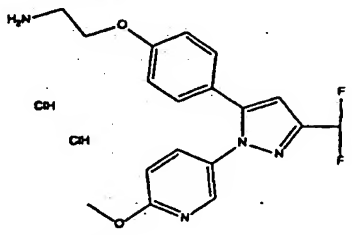
Example 193



(E0193)

This compound was obtained according to a similar manner to that of E0187 as an oil.
NMR(CDCl3), 1.28(3H, d, J=6.6 Hz), 1.45(9H, s), 3.82(3H, s), 3.92(2H, d, J=4.1 Hz), 3.90-4.14(1H, m), 6.67(1H, s), 6.84(2H, d, J=8.9 Hz), 6.86(2H, d, J=9.0 Hz), 7.13(2H, d, J=8.9 Hz), 7.23(2H, d, J=9.0 Hz).
MS(ESI+), 514.2(M+Na).

Example 194

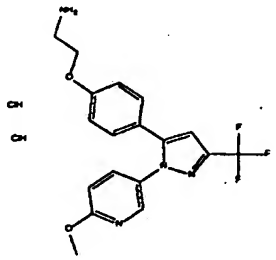


(E0194)

4M HCl/AcOEt 1ml was added to a solution of E0187 (129mg) in AcOEt 1ml, and the mixture was stirred at ambient temperature for 1hour. The supernatant was removed by decantation. The residual oily solid was washed with AcOEt 1ml by decantation. To the residue was added acetone 2ml, and oily residual solid became white powder on stirring. This was stirred at ambient temperature for 20minutes. The precipitates were collected and washed with acetone to give E0194 (91.4mg) as a white powder.
IR (neat) : 2964, 1705, 1668, 1660, 1614, 1581, 1566, 1531, 1512cm-1

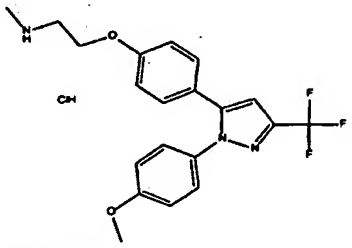
Mass (ESI+) : 361 (M+H)+.
200MHz 1H NMR (DMSO-d6, d) : 3.11-3.23(2H, m), 3.87(3H, s), 4.12-4.28(2H, m), 6.90-7.02(4H, m), 7.11(1H, t, J=54.3 Hz), 7.26(2H, d, J=8.6 Hz), 7.71(1H, dd, J=2.7,8.8 Hz), 8.14(1H, d, J=2.7 Hz), 8.24(2H, brs)

Example 195



(E0195)
This compound was obtained according to a similar manner to that of E0194 as a white powder.
NMR(DMSO-d6), 3.17-3.21(2H, m), 3.95(3H, s), 4.19(2H, t, J=5.0 Hz), 6.93(1H, d, J=8.8 Hz), 7.00(2H, d, J=8.8 Hz), 7.15(1H, s), 7.28(2H, d, J=8.8 Hz), 7.76(1H, dd, J=8.8, 2.6 Hz), 8.18(1H, d, J=2.6 Hz).
MS(ESI+), 379.1(MH+).
IR(KBr), 1612.2cm-1.

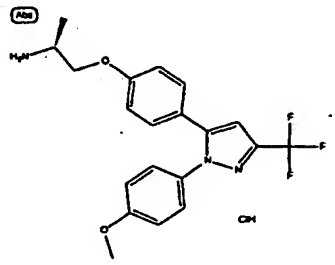
Example 196



(E0196)
This compound was obtained according to a similar manner to that of E0194 as a white powder.
NMR(DMSO-d6), 2.60(3H, s), 3.28-3.33(2H, m), 3.79(3H, s), 4.25(2H, t, J=4.7 Hz), 7.04-6.96(4H, m), 7.09(1H, s), 7.22-7.31(4H, m).
MS(ESI-), 426.2 (M+Cl)+.
IR(KBr); 1610.2, 1515.8cm-1.

MP; 189 - 189.2℃.

Example 197



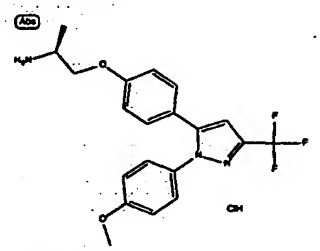
(E0197)

This compound was obtained according to a similar manner to that of E0194 as a white amorphous.

NMR(DEMSO-d6),1.04(3H, d, J=6.0 Hz), 3.5-3.7(1H, m), 3.79(3H, s), 3.98(1H, dd, J=10.1, 6.9 Hz), 4.11(1H, dd, J=10.1, 6.5 Hz), 6.96-7.04(4H, m), 7.09(1H, s), 7.22-7.31(4H, m).

MS(ESI+), 392.2(MH+).

Example 198



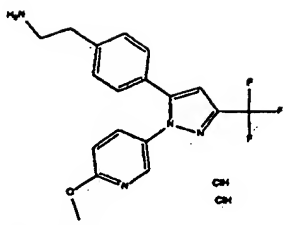
(E0198)

This compound was obtained according to a similar manner to that of E0194 as a white amorphous.

NMR(DEMSO-d6),1.04(3H, d, J=6.0 Hz), 3.5-3.7(1H, m), 3.79(3H, s), 3.98(1H, dd, J=10.1, 6.9 Hz), 4.11(1H, dd, J=10.1, 6.5 Hz), 6.96-7.04(4H, m), 7.09(1H, s), 7.22-7.31(4H, m).

MS(ESI+), 392.2(MH+). IR(Neat) 1612.2cm-1.

Example 199



(E0199)

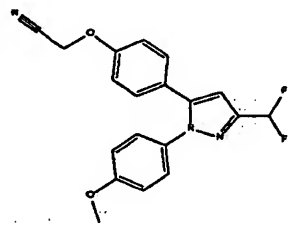
This compound was obtained according to a similar manner to that of E0194 as a white powder.

NMR(DMSO-d6); 2.84-3.20(4H, m), 3.88(3H, s), 6.93(1H, d, J=8.9 Hz), 7.19(1H, s), 7.30-7.36(4H, m), 7.86(1H, dd, J=8.9, 2.7 Hz), 8.19(1H, d, J=2.7 Hz).

MS(ESI+); 363.3(MH+).

IR(KBr); 1612.2, 1500.3cm-1.

Example 200



(E0200)

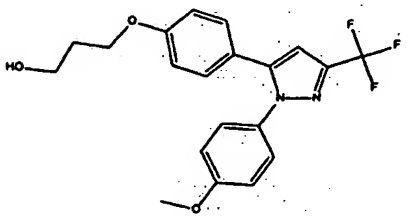
A mixture of P0012 (0.5 g), Chloroacetonitrile (0.2 ml), potassium iodide (525 mg), and potassium carbonate (437 mg) in N,N-dimethylformamide (6 ml) was stirring at 75℃ for 6 hours.

After cooling to room temperature, the mixture was quenched with water, and extracted with ethyl acetate (x3). The combined organic layers were washed with water (x3) and brine, dried over magnesium sulfate, and evaporated to give E0200 as a solid (631.6 mg, 112%).

NMR(CDCl3), 3.83(3H, s), 4.77(2H, s), 6.69(1H, s), 6.76(1H, t, J=55 Hz), 6.96-6.86(4H, m), 7.18-7.24(4H, m).

MS(ESI+), 378.1(M+Na).

Example 201



(E0201)

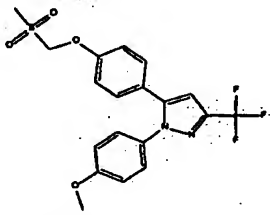
This compound was obtained according to a similar manner to that of E0200 as an oil.

NMR(CDCl3); 1.63(1H, t, J=5.2 Hz), 1.99-2.11(2H, m), 3.82(3H, s), 3.82-3.91(2H, m), 4.12(2H, t, J=6.0 Hz), 6.67(1H, s), 6.84(2H, d, J=8.8 Hz), 6.87(2H, d, J=8.9 Hz), 7.13(2H, d, J=8.8 Hz), 7.32(2H, d, J=8.9 Hz).

IR(Neat); 1612, 1514cm-1.

MS(ESI+); 393.1(MH+), 415.1(M+Na).

Example 202



(E0202)

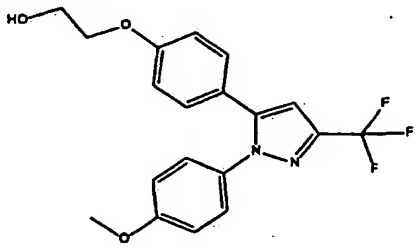
This compound was obtained according to a similar manner to that of E0200 as an oil.

NMR(CDCl3);3.03(3H, s), 3.83(3H, s), 4.97(2H, s), 6.70(1H, s), 6.88(2H, d, J=9.0 Hz), 7.01(2H, d, J=8.8 Hz), 7.17-7.26(4H, m).

IR(KBr); 1612.2, 1513.9 cm-1.

MS(ESI+),449.1(M+Na).

Example 203

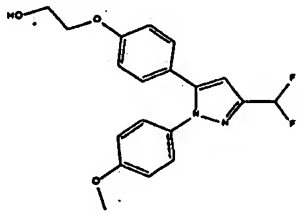


(E0203)

This compound was obtained according to a similar manner to that of E0200 as a white solid.

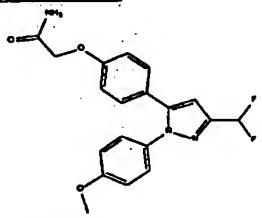
NMR(DMSO-d6), 3.65-3.73(2H, m), 3.79(3H, s), 3.98(2H, t, J=4.7 Hz), 4.87(1H, t, J=5.4 Hz), 6.93(2H, d, J=8.7 Hz), 7.00(2H, d, J=8.9 Hz), 7.07(1H, s), 7.19(2H, d, J=8.7 Hz), 7.28(2H, d, J=8.9 Hz).
MS(ESI+), 401.2(M+Na).
IR(KBr); 1610.3, 1511.9cm-1.

Example 204



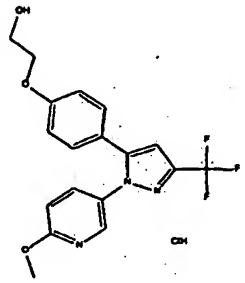
(E0204)
This compound was obtained according to a similar manner to that of E0200 as a white solid.
NMR(CDCl3), 2.01(1H, t, J=6.1 Hz), 3.82(3H, s), 3.93-4.10(4H, m), 6.66(1H, s), 6.76(1H, t, J=55.1 Hz), 6.85(2H, d, J=8.7 Hz), 6.87(2H, d, J=9.0 Hz), 7.15(2H, d, J=8.7 Hz), 7.21(2H, d, J=9.0 Hz).
MS(ESI+); 383.2(M+Na).
IR(KBr); 1610.3, 1513.9, 1454.1cm-1.

Example 205



(E0205)
This compound was obtained according to a similar manner to that of E0200 as a white powder.
NMR(DMSO-d6); 3.78(3H, s), 4.43(2H, s), 6.80-7.53(12H, m, NH2),
MS(ESI+);396.3(M+Na)+.
IR(KBr); 1681.6, 1606.4cm-1.

Example 206



(E0206)

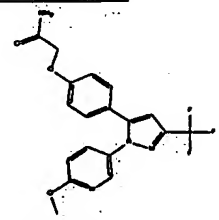
Alkylation of this compound was achieved by a similar manner to that of E0200 to give salt free compound as an oil. Hydrogen chloride salt formation was achieved successively by a similar manner to that of E0172 to give E0206 as a white powder (498.7 mg, 49.6%).

NMR(DMSO-d6), 3.69(2H, t, J=5.0 Hz), 3.88(3H, s), 3.99(2H, t, J=5.0 Hz), 6.92(1H, d, J=8.7 Hz), 6.96(2H, d, J=8.8 Hz), 7.13(1H, s), 7.23(2H, d, J=8.8 Hz), 7.53(1H, dd, J=8.7, 2.9 Hz), 8.18(1H, d, J=2.9 Hz).

MS(ESI+), 402.1(M+Na)+, (Free).

IR(Neat), 1614, 1552cm-1.

Example 207



(E0207)

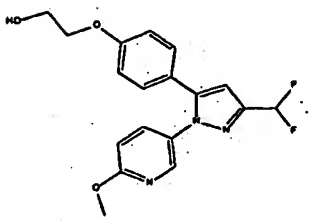
This compound was obtained according to a similar manner to that of E0200 as a white solid.

NMR(CDCl3); 3.88(3H, s), 4.45(2H, s), 6.92(1H, d, J=8.9 Hz), 6.96(2H, d, J=8.8 Hz), 7.14(1H, s), 7.26(2H, d, J=8.8 Hz), 7.41(1H, brs, NH2), 7.56(1H, brs, NH2), 7.76(1H, dd, J=8.9, 2.5 Hz), 8.18(1H, d, J=2.5 Hz).

MS(ESI+); 415.1(M+Na).

IR(KBr); 1693.2, 1608.3cm-1.

Example 208



(E0208)

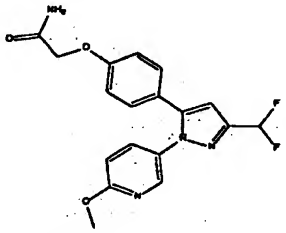
This compound was obtained according to a similar manner to that of E0200 as an oil.

NMR(CDCl3); 3.94(3H, s), 3.94-4.14(4H, m), 6.68(1H, s), 6.74(1H, d, J=8.7 Hz), 6.86(1H, t, J=55.0 Hz), 6.88(2H, d, J=8.9 Hz), 7.16(2H, d, J=8.9 Hz), 7.53(1H, dd, J=2.6, 8.7 Hz), 8.08(1H, d, J=2.6 Hz).

MS(ESI+); 384.2(M+Na).

IR(KBr), 1805.1, 1612.2cm-1.

Example 209



(E0209)

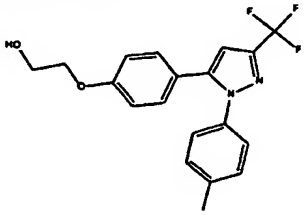
This compound was obtained according to a similar manner to that of E0200 as a white powder.

NMR(DMSO-d6); 3.88(3H, s), 4.44(2H, s), 6.98-9.89(4H, m), 7.10(1H, t, J=54.3 Hz), 7.24(2H, d, J=8.8 Hz), 7.39(1H, brs, NH2), 7.54(1H, brs, NH2), 7.70(1H, dd, J=8.9, 2.8 Hz), 8.14(1H, d, J=2.8 Hz).

MS(ESI-); 373 (M-H)+.

IR(KBr); 1662.3, 1610.3cm-1.

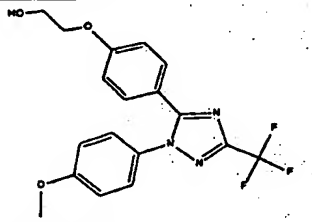
Example 210



(E0210)

This compound was obtained according to a similar manner to that of E0203.
IR (film): 3388.3, 1494.6, 1236.2, 1160.9, 1133.9, 1095.4, 975.8, 833.1 cm-1.

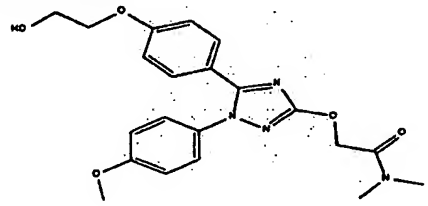
Example 211



(E0211)

E0211 was obtained according to a similar manner to that of E0200.
1H NMR (DMSO-d6, ppm) d 3.62-3.78(2H, m), 3.83(3H, s), 3.93-4.10(2H, m), 4.88(1H, t, J=5.5 Hz), 6.90-7.03(2H, m), 7.03-7.18(2H, m), 7.35-7.58(4H, m),
MS (ESI, m/e) 380(M+1)

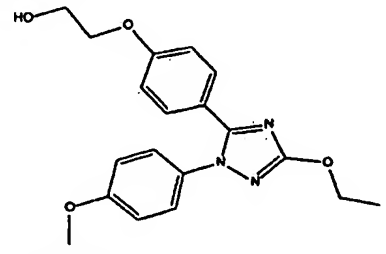
Example 212



(E0212)

E0212 was obtained according to a similar manner to that of E0200.
1H NMR (CDCl3, ppm) d 2.98(3H, s), 3.07(3H, s), 3.84(3H, s), 3.90-4.01(2H, m), 4.02-4.15(2H, m), 5.00(2H, s), 6.75-6.97(4H, m), 7.19-7.30(2H, m), 7.31-7.57(2H, m),
MS (ESI, m/e) 413(M+1)

Example 213

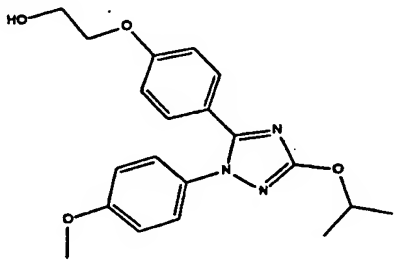


(E0213)

E0213 was obtained according to a similar manner to that of E0200.

1H NMR (CDCl3, ppm) d 1.45(3H, t, J=7.0 Hz), 3.84(3H, s), 3.92-4.00(2H, m), 4.02-4.11(2H, m), 4.39(2H, q, J=7.0 Hz), 6.80-6.88(2H, m), 6.89-6.97(2H, m), 7.22-7.31(2H, m), 7.38-7.48(2H, m),
MS (ESI, m/e) 356(M+1)

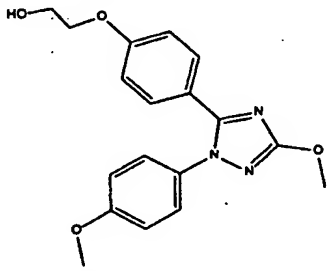
Example 214



(E0214)

E0214 was obtained according to a similar manner to that of E0200.
1H NMR (CDCl3, ppm) d 1.43(6H, d, J=6.1 Hz), 2.15(1H, t, J=6.2 Hz), 3.84(3H, s), 3.89-4.01(2H, m), 4.01-4.13(2H, m), 5.02(1H, 7th, J=6.1 Hz), 6.77-6.99(4H, m), 7.20-7.35(2H, m), 7.37-7.50(2H, m),
MS (ESI, m/e) 370(M+1)

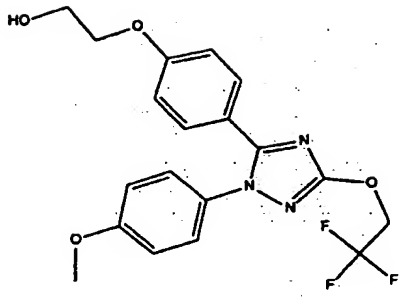
Example 215



(E0215)

E0215 was obtained according to a similar manner to that of E0200.
1H NMR (CDCl3, ppm) d 3.84(3H, s), 3.97-4.00(2H, m), 4.00-410(5H, m), 6.78-6.87(2H, m), 6.89-6.99(2H, m), 7.20-7.33(2H, m), 7.50-7.48(2H, m),
MS (ESI, m/e) 342(M+1)

Example 216



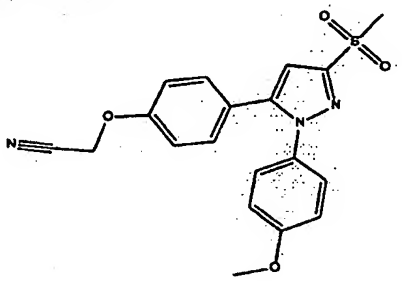
(E0216)

E0216 was obtained according to a similar manner to that of E0200.

1H NMR (CDCl3, ppm) d 3.85(3H, s), 3.90-4.03(2H, m), 4.05-4.17(2H, m), 4.74(2H, q, J=8.2 Hz), 6.79-7.00(4H, m), 7.21-7.32(2H, m), 7.38-7.49(2H, m),

MS (ESI, m/e) 410(M+1)

Example 217

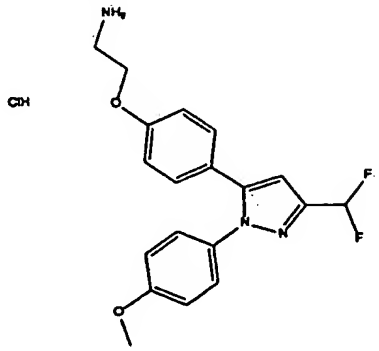


(E0217)

This compound was obtained according to a similar manner to that of E0200.

Mass;384(M+1)

Example 218



(E0218)

To a suspension of lithium aluminum hydride (250 mg) in ether (5 ml) was added E0200 (630 mg) in tetrahydrofuran (1 ml) under ice-bath. After stirring at room temperature for 1 hour. the mixture was quenched with water (0.125 ml), sodium hydroxide aqueous solution (15%, 0.125 ml), and water (0.375 ml), and then stirred at room temperature for 30 minutes. Magnesium sulfate and celite was added to the mixture, then the suspension was filtered and washed with ether. The filtrate was evaporated to give 0.5 g of oil. The oil was purified with column chromatography (SiO_2, 50 ml, eluted with methanol / dichloromethane / concentrated ammonia water (1/10/0.05)) to give oil (300 mg).

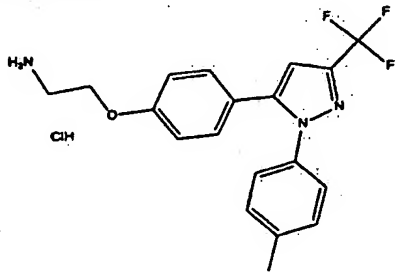
The oil was dissolved in ethyl acetate and added a solution of hydrogen chloride in ethyl acetate (4N, 1.6 ml). The mixture was evaporated to give oil, which was crystallized from methanol and diisopropyl ether to give E0218 as a powder (300 mg, 42.7%)

NMR(DMSO-d6), 3.20(2H, t, J=4.9 Hz), 3.78(3H, s), 4.16(2H, t, J=4.9 Hz), 6.85(1H, s), 6.94-7.01(4H, m), 7.08(1H, t, J=54.6 Hz), 7.20-7.26(4H, m).

MS(ESI+), 360.3(MH+, free).

IR(KBr, 20727-7), 1612, 1513.9 cm-1.

Example 219

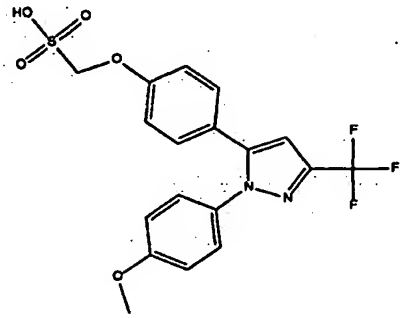


(E0219)

This compound was obtained according to a similar manner to that of E0218.

IR (film): 3401.8, 1610.3, 1511.9, 1469.5, 1240.0, 1162.9, 1130.1, 975.8, 827.3 cm-1.

Example 220



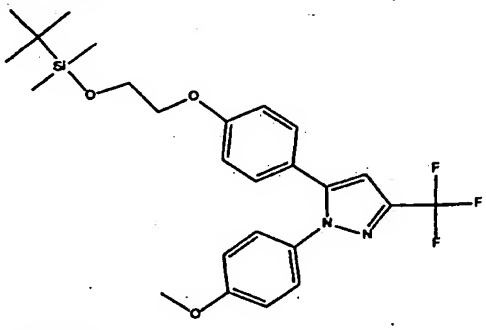
(E0220)

A mixture of P0011 (200 mg), Chloromethylsulfonic acid sodium salt (274 mg), potassium iodide (298 mg), and potassium carbonate (248 mg) in 1-methyl-2-pyrrolidinone (2 ml) was stirring at 150℃ overnight. After cooling to room temperature, the mixture was poured into a mixture of aqueous hydrogen chloride solution (1 N), brine, and ethyl acetate. The aqueous layer was separated and extracted with ethyl acetate (x3). The combined organic layers were dried over magnesium sulfate, and evaporated under reduced pressure to give oil. The oil was purified with column chromatography (SiO2 100 ml, eluted with 15% methanol / dichloromethane) to give E0220 as a brown amorphous (154.3 mg, 60%)

MS(ESI-); 427.1(M-H).

NMR(DMSO-d6), 3.79(3H, s), 4.52(2H, s), 7.00(2H, d, J=9.0 Hz), 7.01(2H, d, J=8.9 Hz), 7.07(1H, s), 7.18(2H, d, J=9.0 Hz), 7.27(2H, d, J=8.9 Hz).

Example 221

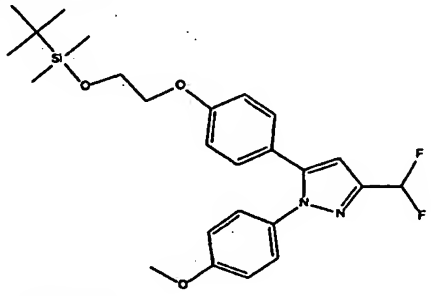


(E0221)

To a solution of P0011 (1.0g) in DMF (10ml) under water cooling was added portionwise NaH (60%in Oil, 144mg) and stirred for 1 hour. After then, III (787mg) was added and the reaction mixture was stirred at 50oC for 5 hours. The mixture was quenched with water and extracted twice with EtOAc. The organic layer was washed

three times with water and once with brine, dried over MgSO4, filtered and evaporated under reduced pressure. The residue was column chromatographed on silica gel (50ml) to give 803mg (55%) of E0221 as a oil.

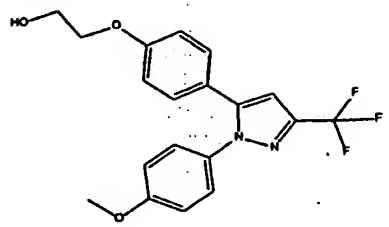
Example 222



(E0222)

This compound was obtained according to a similar manner to that of E0221.

Example 223

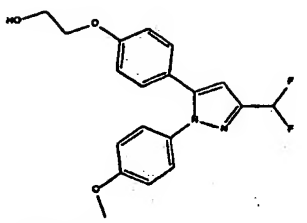


(E0223)

The mixture of E0221 (800mg) and cHCl (100ul) in EtOH (10ml) was stirred at room temperature for 3 hours. After addition of aqueous sodium bicarbonate, the mixture was evaporated, and extracted twice with EtOAc. The organic layer was washed with water and brine, dried over MgSO4, filtered and evaporated under reduced pressure. The residue (710mg) was column chromatographed on silica gel (50ml) to give 570mg (93%) of E0223.

IR (film): 3409.5, 1612.2, 1513.9, 1467.6, 1243.9, 1162.9, 1130.1, 835.0, 835.0 cm-1.

Example 224



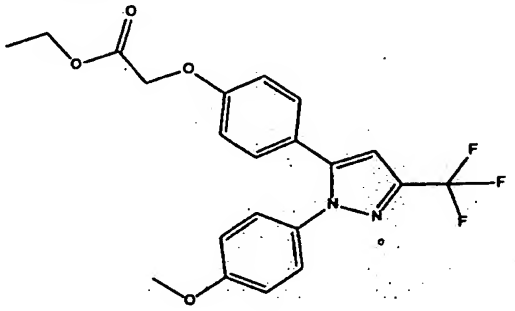
(E0224)

This compound was obtained according to a similar manner to that of E0223.

mp: 122.3-122.5℃

IR (film): 3399.9, 1612.2, 1513.9, 1456.0, 1251.6, 1174.4, 1083.8, 1033.7, 836.9, 800.3 cm-1.

Example 225



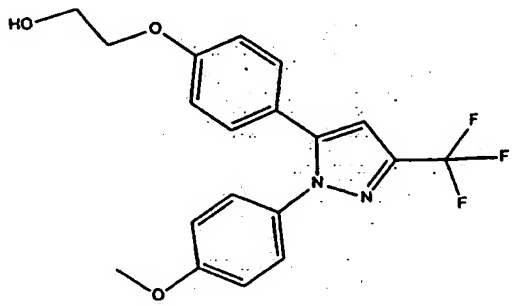
(E0225)

60% Sodium hydride 39.7mg was added to a solution of P0011 (255mg) in DMF 1.5ml. The mixture was stirred at ambient temperature for 1hour. To this was added ethyl bromoacetate 153mg. The reaction mixture was stirred at ambient temperature for 1hour, and then quenched by adding saturated ammonium chloride solution, and whole mixture was extracted with AcOEt. The organic layer was washed with H2O, aqueous sodium chloride solution, dried over magnesium sulfate, and concentrated in vacuo. The residue was purified by silica gel column chromatography eluted with AcOEt / n-hexane = 30% to give E0225 (217mg) as an oil.

Mass (ESI+) 421(M+H)+

200MHz 1H NMR (DMSO-d6, d) : 1.94(3H, t, J=7.1 Hz), 3.79(3H, s), 4.15(2H, q, J=7.1 Hz), 4.79(2H, s), 6.92(2H, d, J=8.8 Hz), 6.99(2H, d, J=8.9 Hz), 7.09(1H, s), 7.20(2H, d, J=8.8 Hz), 7.28(2H, d, J=8.9 Hz)

Example 226



(E0226)

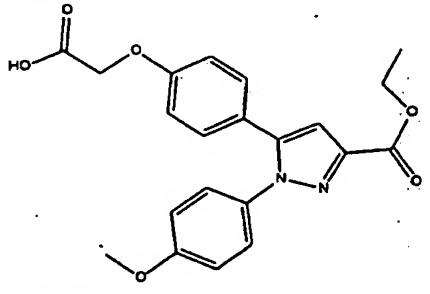
1M solution of diisobutylaluminum hydride in toluene 0.5ml was added dropwise to a solution of E0225 (98mg) in THF 3ml at -50℃. The mixture was stirred at -50℃ for 1hour, then at 5℃ for 1hour. Additional 1M solution of diisobutylaluminum hydride in toluene 0.5ml was added dropwise. After stirring at 5℃ for one more hour, the reaction was quenched by adding 10% aqueous potassium sodium tartaric acid salt, and the mixture was filtered through a celite pad. The filtrate was extracted with AcOEt. The organic layer was washed with saturated aqueous sodium chloride solution, dried over magnesium sulfate, and concentrated in vacuo. The residue was purified by preparative thin layer silica gel chromatography developed by AcOEt / n-hexane = 60%. The separated silica gel was extracted with 10% MeOH/CHCl3 and the solvent was evaporated in vacuo to give E0226 (54.5mg) as an oil, which became solid on standing.

IR (KBr) : 3431, 2931, 1612, 1564, 1549, 1512cm-1

Mass (ESI+) : 379 (M+H)+

400MHz 1H NMR (DMSO-d6, d) : 3.67-3.72(2H, m), 3.79(3H, s), 3.84-3.99(2H, m), 4.87(1H, t, J=5.4 Hz), 6.93(2H, d, J=8.7 Hz), 7.00(2H, d, J=8.9 Hz), 7.10(1H, s), 7.19(2H, d, J=8.7 Hz), 7.27(2H, d, J=8.9 Hz)

Example 227



(E0227)

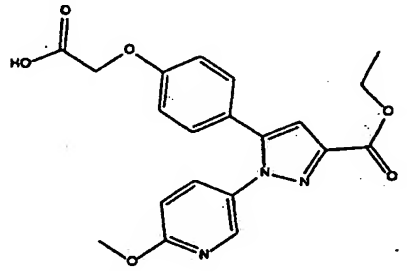
60% Sodium hydride 52mg was added to a solution of P0020 (200mg) in DMF 2ml

under ice bath cooling. The mixture was stirred at same temperature for 30minutes. To this was added bromoacetic acid 90.3mg. The reaction mixture was stirred at ambient temperature for 2hours, and then quenched by adding s1M HCl 3ml. H2O 3ml and diisopropyl ether 2ml were added and the mixture was stirred in an ice bath for 30minutes. The precipitates were collected and washed with H2O and diisopropyl ether to give FR274679 231.2mg as a white powder

Mass (ESI+) : 397 (M+H)+

200MHz 1H NMR (DMSO-d6, d) : 1.31(3H, t, J=7.1 Hz), 3.79(3H, s), 4.32(2H, q, J=7.1 Hz), 4.68(2H, s), 6.88(2H, d, J=8.8 Hz), 7.00(2H, d, J=8.9 Hz), 7.02(1H, s), 7.18(2H, d, J=8.8 Hz), 7.26(2H, d, J=8.9 Hz), 13.05(1H, brs)

Example 228



(E0228)

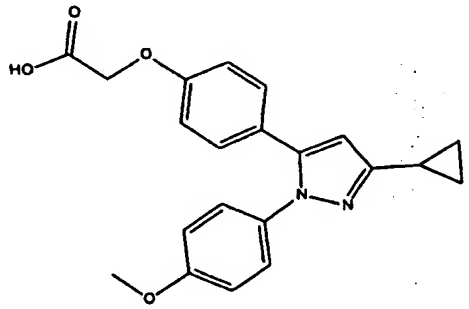
E0228 was prepared in a similar manner to that of E0227.

white powder

Mass (ESI+) : 398 (M+H)+

200MHz 1H NMR (DMSO-d6, d) : 1.31(3H, t, J=7.1 Hz), 3.88(3H, s), 4.33(2H, q, J=7.1 Hz), 4.70(2H, s), 6.92(2H, d, J=8.8 Hz), 6.89-7.00(1H, m), 7.06(1H, s), 7.22(2H, d, J=8.8 Hz), 7.73(1H, dd, J=2.8,8.8 Hz), 8.15(1H, d, J=2.8 Hz), 13.04(1H, brs)

Example 229



(E0229)

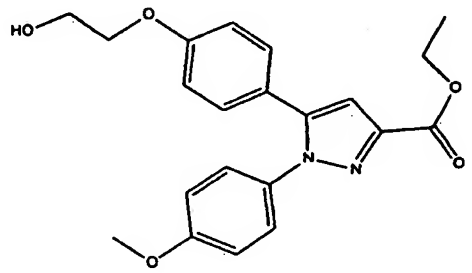
E0229 was prepared from P0034 in a similar manner to that of E0227.

oil

Mass (ESI+) : 365 (M+H)+

200MHz 1H NMR (DMSO-d6, d) : 0.70-0.93(4H, m), 1.70-2.00(1H, m), 3.76(3H, s), 4.66(2H, s), 6.25(1H, s), 6.85(2H, d, J=8.9 Hz), 6.92(2H, d, J=9.0 Hz), 7.06-7.16(4H, m), 13.00(1H, brs)

Example 230



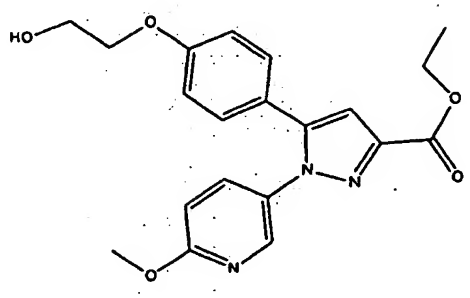
(E0230)

To a suspension of sodium borohydride 19.1mg in THF 2ml was added boron trifluoride diethyl etherate 89.5mg dropwise under ice bath cooling 2.5eq. The mixture was stirred at same temperature for 30minutes. E0227 (100mg) was added in one portion and the mixture was stirred at ambient temperature for 5hours. 1M HCl 5ml was added and the mixture was stirred at ambient temperature for 30minutes. The mixture was extracted with AcOEt. The organic layer was washed with saturated aqueous sodium bicarbonate solution and saturated aqueous sodium chloride solution, dried over magnesium sulfate, and concentrated in vacuo. The residue was crystallized from diisopropyl ether to give E0230 (68.9mg) as a white powder.

Mass (ESI+) : 383 (M+H)+

200MHz 1H NMR (DMSO-d6, d) : 1.31(3H, t, J=7.1 Hz), 3.65-3.73(2H, m), 3.79(3H, s), 3.94-4.00(2H, m), 4.32(2H, q, J=7.1 Hz), 4.87(1H, t, J=5.5 Hz), 6.91(2H, d, J=8.8 Hz), 6.99(2H, d, J=8.9 Hz), 7.01(1H, s), 7.17(2H, d, J=8.8 Hz), 7.25(2H, d, J=8.9 Hz)

Example 231



(E0231)

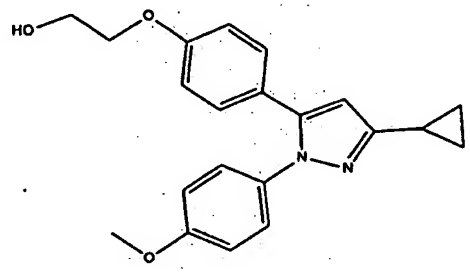
E0231 was prepared in a similar manner to that of E0230.

white powder

Mass (ESI+) : 384 (M+H)+

200MHz 1H NMR (DMSO-d6, d) : 1.31(3H, t, J=7.1 Hz), 3.65-3.74(2H, m), 3.88(3H, s), 3.96-4.02(2H, m), 4.33(2H, q, J=7.1 Hz), 4.87(1H, t, J=5.4 Hz), 6.89-6.96(3H, m), 7.05(1H, s), 7.21(2H, d, J=8.7 Hz), 7.72(1H, dd, J=2.7,8.8 Hz), 8.14(1H, d, J=2.7 Hz)

Example 232



(E0232)

E0232 was prepared in a similar manner to that of E0230.

white powder

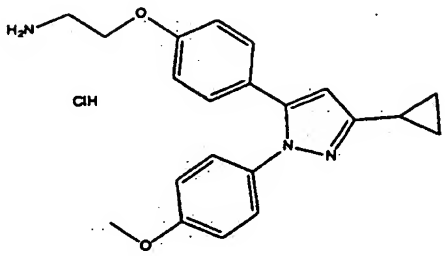
mp. 142-144℃

IR (KBr) : 3246, 2924, 1612, 1566, 1547, 1516cm-1

Mass (ESI+) : 351 (M+H)+

200MHz 1H NMR (DMSO-d6, d) : 0.68-0.77(2H, m), 0.85-0.95(2H, m), 1.92(1H, m), 3.64-3.73(2H, m), 3.76(3H, s), 3.96(2H, t, J=4.9 Hz), 4.85(1H, t, J=5.5 Hz), 6.24(1H, s), 6.85-6.96(4H, m), 7.05-7.17(4H, m)

Example 233



(E0233)

E0233 was prepared in a similar manner to that of E0230.

white powder

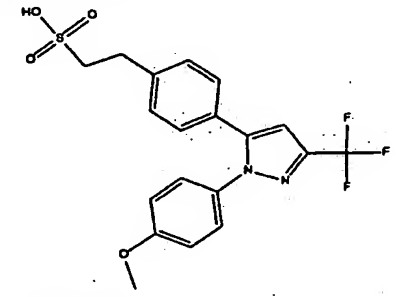
mp. 228-231℃

IR (KBr) : 3082, 2958, 2885, 2802, 2733, 2480, 1606, 1572, 1512cm-1

Mass (ESI+) : 350 (M+H)+

200MHz 1H NMR (DMSO-d6, d) : 0.69-0.77(2H, m), 0.83-0.96(2H, m), 1.93(1H, m), 3.14-3.22(2H, m), 3.76(3H, s), 4.14-4.20(2H, m), 6.27(1H, s), 6.93(4H, d, J=8.8 Hz), 7.14(4H, d, J=8.8 Hz), 8.24(2H, brs)

Example 234



(E0234)

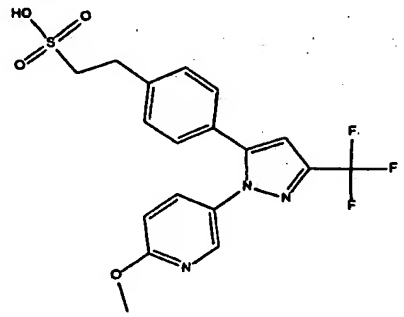
A solution of sodium sulfite 84.2mg in H2O 1ml was added to a solution of P0022 (258.1mg) in EtOH 3ml and stirred at 70℃ for 2hours. At which time, white precipitates were appeared and H2O 1ml was added to dissolve the precipitates. The mixture was stirred at 80℃ overnight to give a clear solution. This was stirred at 80℃ further for 28hours. The reaction mixture was acidified by 1M HCl 0.7ml, concentrated and dried under vacuo. The residue was dissolved in CHCl3, dried over magnesium sulfate, all of unsoluble matter was filtered off, and concentrated in vacuo to give E0234 (245mg) as an amorphous powder.

Mass (API-ES negative) 425(M-H)+

200MHz 1H NMR (DMSO-d6, d) : 2.61-2.69(2H, m), 2.78-2.91(2H, m), 3.79(3H, s), 7.00(2H, d, J=8.9 Hz), 7.12(1H, s), 7.17(2H, d, J=8.6 Hz), 7.22(2H, d, J=8.6 Hz),

7.29(2H, d, J=8.9 Hz)

Example 235



(E0235)

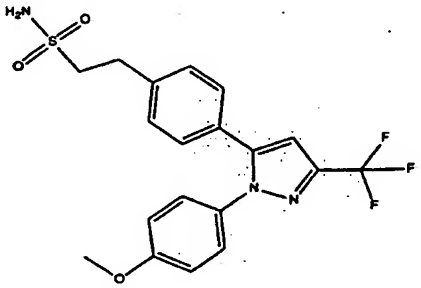
E0235 was prepared from P0023 in a similar manner to that of E0234.

amorphous powder

Mass (API-ES negative) : 426 (M-H)+.

200MHz 1H NMR (DMSO-d6, d) : 2.61-2.69(2H, m), 2.83-2.92(2H, m), 3.88(3H, s), 6.92(1H, d, J=8.8 Hz), 7.17(1H, s), 7.23(4H, s), 7.75(1H, dd, J=8.8,2.7 Hz), 8.20(1H, d, J=2.7 Hz)

Example 236



(E0236)

DMF 41mg was added to a solution of E0234 (239mg) in thionyl chloride 0.6ml and the mixture was stirred at 50℃ for 30minutes. The reaction mixture was concentrated in vacuo. To the residue was added toluene 3ml, and concentrated in vacuo. The residue was dissolved in THF 10ml and was added dropwise to a solution of 28% aqoueous ammonium hydroxide solution 0.5ml and tetrabutylammonium hydrogensulfate 19mg in THF 4ml under ice bath cooling. After stirring at ambient temperature for 30minutes, the reaction mixture was partitioned between AcOEt and aqueous sodium chloride solution. The organic layer was washed with aqueous sodium chloride solution, dried

over magnesium sulfate. The residue was purified by silica gel column chromatography eluted with MeOH / CHCl3 = 2%, 5%. Pure fraction was collected and concentrated in vacuo. The residual solid was recrystallized from EtOH-diisopropyl ether to give E0236 (72.6mg) as a white powder.

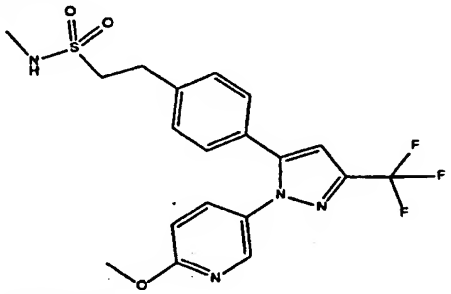
mp. 131-132℃

IR (KBr) : 3354, 3184, 3126, 1707, 1693, 1676, 1647, 1564, 1549, 1516cm-1

Mass (ESI+) : 426 (M+H)+

200MHz 1H NMR (DMSO-d6, d) : 2.95-3.04(2H, m), 3.21-3.30(2H, m), 3.79(3H, s), 6.87(2H, s), 7.00(2H, d, J=8.9 Hz), 7.14(1H, s), 7.23-7.33(6H, m)

Example 237



(E0237)

E0237 was prepared in a similar manner to that of E0236.

white powder

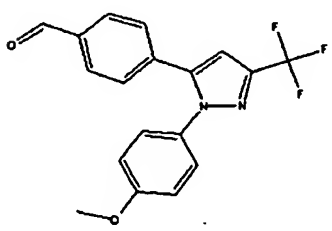
mp. 139-140℃

IR (KBr) : 3230, 3132, 1610, 1568, 1527, 1500cm-1

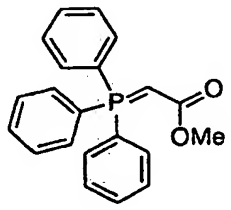
Mass (ESI+) : 441 (M+H)+

200MHz 1H NMR (DMSO-d6, d) : 2.58(3H, s), 2.90-3.00(2H, m), 3.25-3.33(2H, m), 3.88(3H, s), 6.93(1H, d, J=8.9 Hz), 6.97(1H, brs), 7.19(1H, s), 7.26(2H, d, J=8.3 Hz), 7.34(2H, d, J=8.3 Hz), 7.77(1H, dd, J=8.9,2.8 Hz), 8.19(1H, d, J=2.8 Hz)

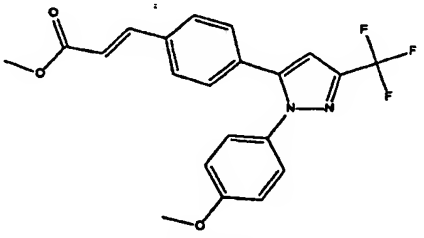
Example 238



(E0238-0)



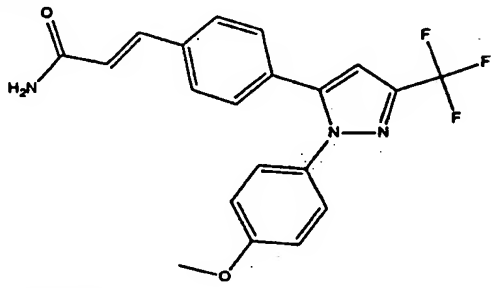
(E0238-1)



(E0238)

A mixture of E0238-0 (800mg) and E0238-1 , methyl (triphenylphosphoranylidene)-acetate (850mg) in toluene (10ml) was stirred under reflux condition for 5 hrs. The mixture was evaporated under reduced pressure and column chromatographed on silica gel (50ml, Hex:EtOAc=5:1) to give 795mg(85.5%) of E0238.
IR (film): 1718.3, 1637.3, 1513.9, 1241.9, 1166.7, 1132.0, 977.7, 837.0cm-1

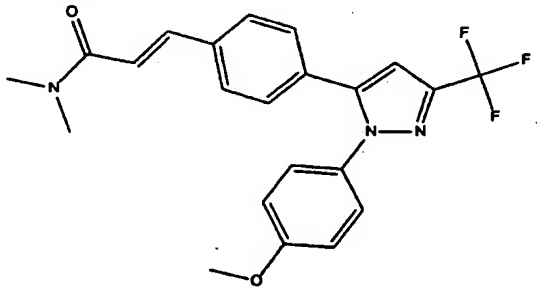
Example 239



(E0239)

T a suspension of E0163 (180mg) in toluene (5ml) was adde thionylchloride (0.17ml) at room temperature. The reaction mixture was stirred at 100℃ for 5 hours until the mixture become clear solution. After then, the mixture was evaporated under reduced pressure. (become solid) THF was added, and then aqueous NH3 (37%) was added. The mixture was stirred for 1 hour, and quenched with water, and extracted twice with EtOAc. The combined organic layer was washed with sat.NaHCO3, water and brine, dried over Na2SO4, filtered and evaporated under reduced pressure to give 170mg (95%) of E0239 as a powder.
IR (KBr): 3347.8, 1671.9, 1606.4, 1513.9, 1467.6, 1388.5, 1236.2, 1164.8, 1132.0, 979.7, 837.0cm-1.

Example 240



(E0240)

T a suspension of E0163 (200mg) in toluene (4ml) was added thionylchloride (0.19ml)

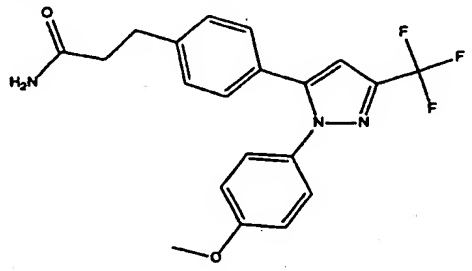
at room temperature. The reaction mixture was stirred at 10°C for 5 hours until the mixture become clear solution. After then, the mixture was evaporated under reduced pressure. (become solid) THF was added, and then Me2NH (116mg) was added. The mixture was stirred for 1 hour, and quenched with water, and extracted twice with EtOAc. The combined organic layer was washed with sat.NaHCO3, water and brine, dried over Na2SO4, filtered and evaporated under reduced pressure to give 45mg (21%) of E0240 as a powder.

Filtrate (58mg).

mp: 118-120°C

IR (film): 1650.8, 1608.3, 1511.9, 1469.5, 1240.0, 1159.0, 1133.9cm-1.

Example 241

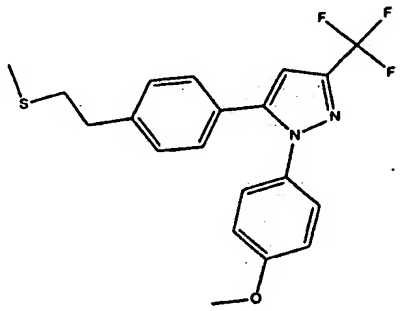


(E0241)

A mixture of E0239 (125mg) and Pd/C (100mg) in EtOH (10m) was stirred under H2 atmosphere for 3.0 hours. After filtration, a filtrate was evaporated under reduced pressure. The residue was dissolved in EtOH and filtered with syringe driven filter, and evaporated to give 85mg of E0241.

IR (KBr): 3342.0, 1670.0, 1511.9, 1240.0, 1160.9, 1130.1cm-1.

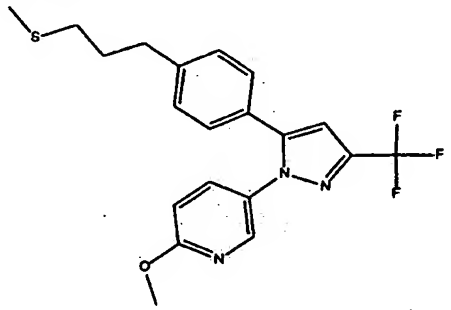
Example 242



(E0242)

A mixture of E0035 (300mg) and MeSNa (72mg) in DMF (6ml) was heated at 70℃ for 5 hours. After cooling, the reaction mixture was partitioned between EtOAc and water. The aqueous layer was separated and extracted with EtOAc. The combined organic layer was washed with water (twice) and brine, dried over Na2SO4, filtered and evaporated. The residue was column chromatographed on silica gel to give 270mg (quant) of E0242.

Example 243



(E0243)

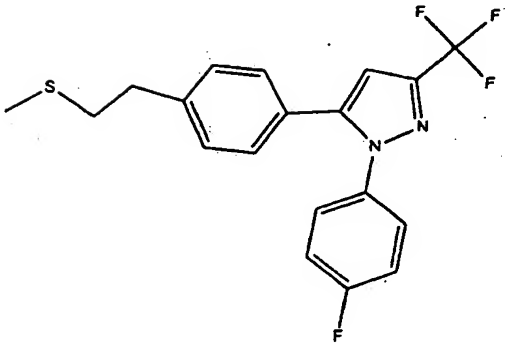
E0243 was prepared from E0038 in a similar manner to that of E0242.

oil

Mass (ESI+) : 408 (M+H)+

200MHz 1H NMR (DMSO-d6, d) : 1.73-1.89(2H, m), 2.03(3H, s), 2.40-2.52(2H, m), 2.62-2.70(2H, m), 3.88(3H, s), 6.92(1H, d, J=8.8 Hz), 7.18(1H, s), 7.24(4H, s), 7.76(1H, dd, J=8.8,2.7 Hz), 8.18(1H, d, J=2.7 Hz)

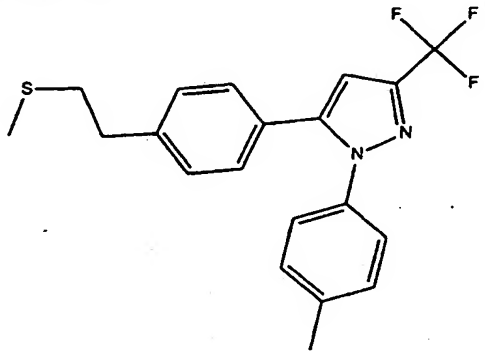
Example 244



(E0244)

This compound was obtained according to a similar manner to that of E0242.

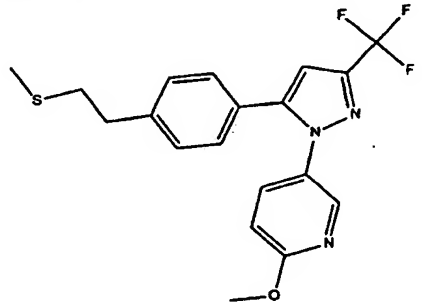
Example 245



(E0245)

This compound was obtained according to a similar manner to that of E0242.

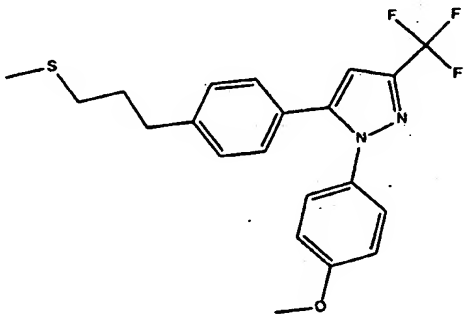
Example 246



(E0246)

This compound was obtained according to a similar manner to that of E0242

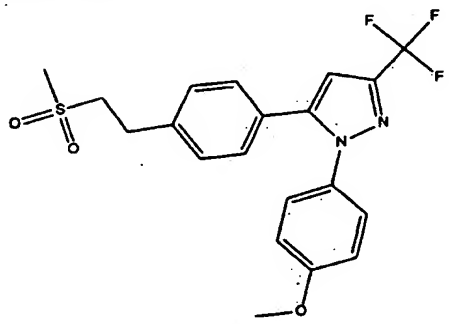
Example 247



(E0247)

This compound was obtained according to a similar manner to that of E0242.

Example 248



(E0248)

A mixture of E0242 (250mg) and mcpba (165mg) in CH2Cl2 was stirred under ice-cooling for 1 hour, and then mcpba (55mg) was added. After stirring for 1 hour under ice cooling, the reaction mixture was partitioned between CHCl3 and sat.NaHCO3. The organic layer was separated , washed with sat.NaHCO3, water and brine, dried over Na2SO4, filtered and evaporated under reduced pressure. The residue was column chromatographed on silica gel (Hex/EtOAc) to give 141mg (52%) of E0248.

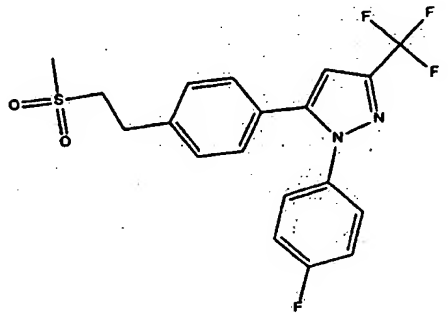
IR (film): 1511.9, 1303.6, 1240.0, 1130.1cm-1.

Oxide: FR267958

NMR (CDCl3): 2.599(s, 3H), 2.85-3.21(m, 4H), 3.828(s, 3H), 6.721(s, 1H), 6.872(d,J=9.0Hz,2H), 7.141(s, 4H), 7.179(d,J=9.0Hz, 2H).

MS: (M+Na)+ 431.1 (M110092-2)

Example 249

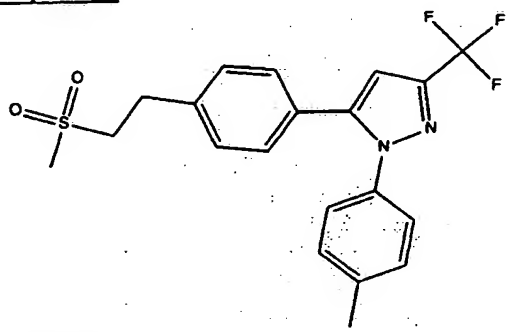


(E0249)

This compound was obtained according to a similar manner to that of E0248.

IR (film): 1511.9, 1469.5, 1311.4, 1282.4, 1236.2, 1126.2, 973.9, 823.5, 759.8 cm-1.

Example 250

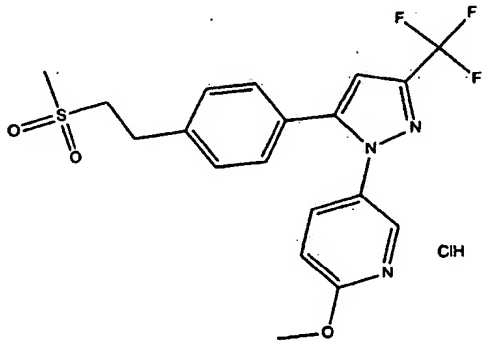


(E0250)

This compound was obtained according to a similar manner to that of E0248.

IR (film): 1511.9, 1469.5, 1311.4, 1282.4, 1236.2, 1128.2, 973.9, 823.5, 759.8cm-1.

Example 251



(E0251)

This compound was obtained according to a similar manner to that of E0248.

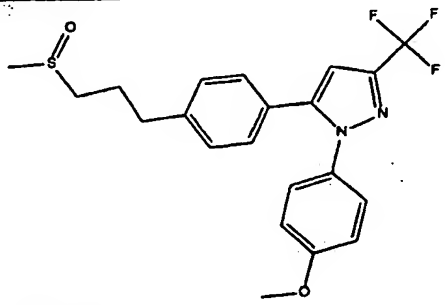
IR(film): 1673.9, 1616.1, 1498.4, 1477.2, 1467.6, 1390.4, 1307.5, 1290.1, 1240.0,

1160.9, 1132.0, 971.9, 756.0cm-1.

NMR (CDCl3): 2.76-2.94(m, 4H), 3.927(s, 3H), 3.943(s, 3H), 6.728(s, 1H), 6.752(d, J=8.9Hz, 1H), 7.12-7.26(m, 4H), 7.46-7.59(m, 1H), 8.04-8.10(m, 1H).

MASS (M+Na)+445.1 (FR267958-N)

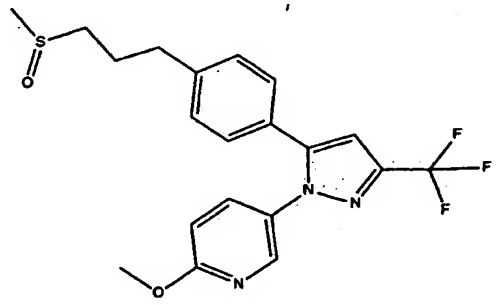
Example 252



(E0252)

To a solution of E0247 (450mg) in dichloromethane (45ml) was added MCPBA (306mg) at room temperature. After stirring for 1 hour, the reaction mixture was washed with sat.NaHCO3 (twice) and water, dried over Na2SO4, filtered and evaporated under reduced pressure. The residue was column chromatographed on silica gel (50ml) to give 470mg of E0252 as an oil.

Example 253



(E0253)

E0253 was prepared in a similar manner to that of E0252.

white powder.

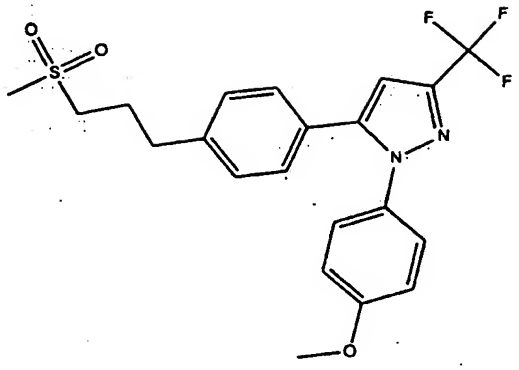
mp. 92-93℃

IR (KBr) : 3080, 2952, 1612, 1566, 1547, 1529, 1500cm-1

Mass (ESI+) : 424 (M+H)+

200MHz 1H NMR (DMSO-d6, d) : 1.87-2.00(2H, m), 2.51(3H, s), 2.56-2.78(4H, m), 3.88(3H, s), 6.92(1H, d, J=8.9 Hz), 7.19(1H, s), 7.21-7.31(4H, m), 7.76(1H, dd, J=2.7,8.9 Hz), 8.19(1H, d, J=2.7 Hz)

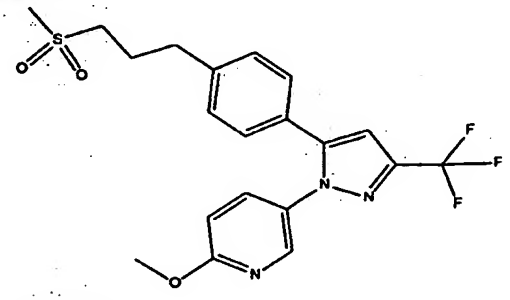
Example 254



(E0254)

To a solution of E0247 (450mg) in dichloromethane (45ml) was added MCPBA (306mg) at room temperature. After stirring for 1 hour, the reaction mixture was washed with sat.NaHCO3 (twice) and water, dried over Na2SO4, filtered and evaporated under reduced pressure. The residue was column chromatographed on silica gel (50ml) and recrystalized from EtOH to give 168mg (44%) of E0254.

Example 255



(E0255)

3-Chloroperoxybenzoic acid (407mg) was added to a solution of E0253 (666.3mg) in CH2Cl2 6ml under ice bath cooling. The reaction mixture was stirred at ambient temperature for 1hour. The mixture was diluted with CHCl3, washed with 1M NaOH, 5% aqueous sodium thiosulfate solution, and saturated aqueous sodium chloride solution, dried over magnesium sulfate, and concentrated in vacuo. The residue was recrystallized from AcOEt-n-hexane to give E0255 (565.2mg) as a white powder.

mp. 121-122℃

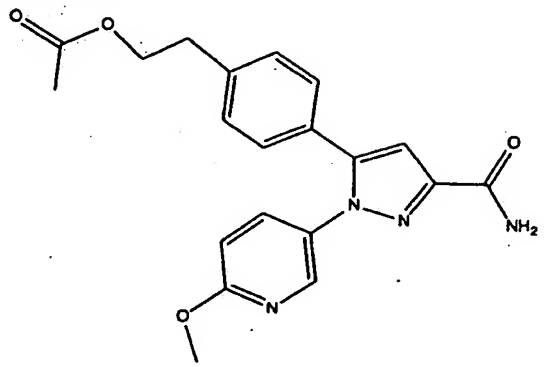
IR (KBr) : 3120, 2954, 1707, 1693, 1647, 1612, 1566, 1547, 1529, 1500cm-1

Mass (ESI+) : 440 (M+H)+

200MHz 1H NMR (DMSO-d6, d) : 1.93-2.06(2H, m), 2.67-2.75(2H, m), 2.96(3H, s), 3.04-3.13(2H, m), 3.88(3H, s), 6.92(1H, d, J=8.8 Hz), 7.19(1H, s), 7.19-7.31(4H, m),

7.76(1H, dd, J=8.8,2.8 Hz), 8.19(1H, d, J=2.8 Hz)

Example 256



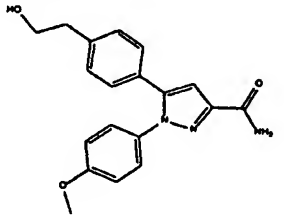
(E0256)

Oxalylchloride 286mg was added to a suspension of E0274 (0.43g) in CH2Cl2 3ml under ice bath cooling. DMF 1drop was added and the mixture was stirred at same temperature for 1hour, and then concentrated in vacuo. To the residue, was added toluene and concentrated in vacuo. The residue was dissolved in THF 5ml and was added to a solution of aqueous ammoniumhydroxide solution 5ml with under ice bath cooling. The mixture was stirred at same temperature for 1hour, diluted with AcOEt, washed successively with 1M HCl, saturated aqueous sodium bicarbonate solution, and saturated aqueous sodium chloride solution, dried over magnesium sulfate, and concentrated in vacuo. The residue was purified by silica gel column chromatography eluted with AcOEt / n-hexane= 60%. The pure fraction was collected and concentrated in vacuo and the residue was crystallized from diisopropylether to give E0256 (287.8mg) as a white powder.

Mass (ESI+) : 381 (M+H)+

200MHz 1H NMR (DMSO-d6, d) : 1.97(3H, s), 2.89(2H, t, J=6.8 Hz), 3.87(3H, s), 4.21(2H, t, J=6.8 Hz), 6.91(1H, d, J=8.8 Hz), 6.98(1H, s), 7.22(2H, d, J=8.4 Hz), 7.28(2H, d, J=8.4 Hz), 7.38(1H, brs), 7.63-7.75(1H, brs), 7.72(1H, dd, J=2.7,8.8 Hz), 8.16(1H, d, J=2.7 Hz)

Example 257



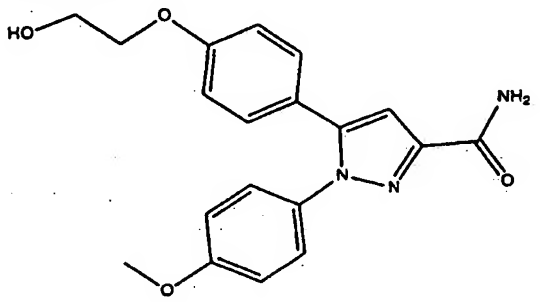
(E0257)

A mixture of E0005 (449.1mg) and sodium methoxide 238mg in formamide 5ml was heated at 70℃ for 5hours. The mixture was allowed to cool to ambient temperature, and was partitioned between ethyl acetate and H2O. The organic layer was washed with saturated aqueous sodium chloride solution, dried over magnesium sulfate, and concentrated in vacuo. The residue was purified by silica gel column chromatography eluted with CHCl3, then MeOH / CHCl3 = 2%, 5% to give E0257 (235.7mg) as a white powder.

Mass (ESI+) : 338(M+H)+

400MHz 1H NMR (DMSO-d6, d) : 2.70(2H, t, J=6.9 Hz), 3.56-3.62(2H, m), 3.79(3H, s), 4.65(1H, t, J=5.1 Hz), 6.92(1H, s), 6.99(2H, d, J=8.9 Hz), 7.15(2H, d, J=8.3 Hz), 7.20(2H, d, J=8.3 Hz), 7.27(2H, d, J=8.9 Hz), 7.33(1H, s), 7.64(1H, s)

Example 258



(E0258)

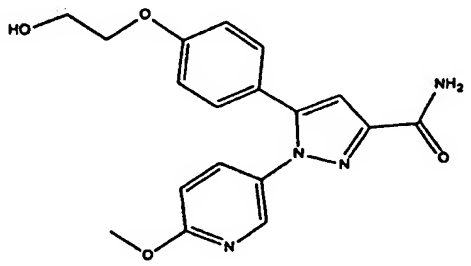
E0258 was prepared in a similar manner to that of E0257.

white powder

Mass (ESI+) : 454 (M+H)+

200MHz 1H NMR (DMSO-d6, d) : 3.65-3.73(2H, m), 3.78(3H, s), 3.94-4.00(2H, m), 4.86(1H, t, J=5.5 Hz), 6.88(1H, s), 6.91(2H, d, J=8.8 Hz), 6.99(2H, d, J=8.9 Hz), 7.16(2H, d, J=8.8 Hz), 7.26(2H, d, J=8.9 Hz), 7.32(1H, s), 7.63(1H, s)

Example 259



(E0259)

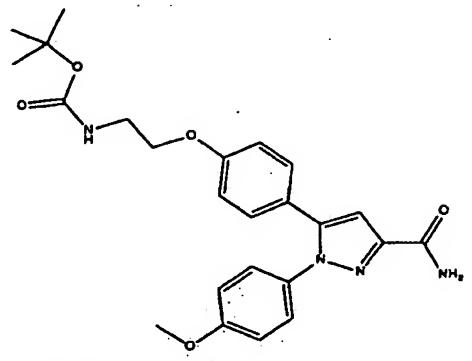
E0259 was prepared in a similar manner to that of E0257.

white powder

Mass (ESI+) : 355 (M+H)+

200MHz 1H NMR (DMSO-d6, d) : 3.65-3.74(2H, m), 3.87(3H, s), 3.96-4.05(2H, m), 4.87(1H, t, J=5.5 Hz), 6.88-6.97(4H, m), 7.20(2H, d, J=8.7 Hz), 7.37(1H, brs), 7.67-7.73(1H, brs, overlapping), 7.71(1H, dd, J=2.6,8.8 Hz), 8.16(1H, d, J=2.6 Hz)

Example 260



(E0260)

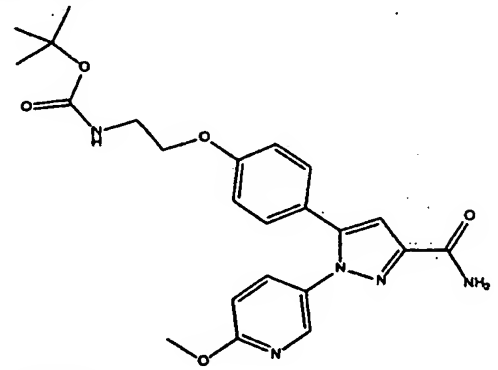
E0260 was prepared in a similar manner to that of E0257.

white powder

Mass (ESI+) : 453 (M+H)+

400MHz 1H NMR (DMSO-d6, d) : 1.37(9H, s), 3.24-3.29(2H, m), 3.78(3H, s), 3.94(2H, t, J=5.8 Hz), 6.88(1H, s), 6.90(2H, d, J=8.8 Hz), 6.99(2H, d, J=9.0 Hz), 6.97-7.00(1H, br), 7.16(2H, d, J=8.8 Hz), 7.25(2H, d, J=9.0 Hz), 7.32(1H, brs), 7.62(1H, brs)

Example 261



(E0261)

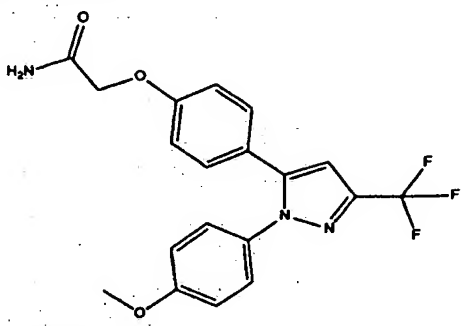
E0261 was prepared in a similar manner to that of E0257.

white powder

Mass (ESI+) : 454 (M+H)+

200MHz 1H NMR (DMSO-d6, d) : 1.37(9H, s), 3.22-3.33(2H, m), 3.88(3H, s), 3.93-3.99(2H, m), 6.88-7.10(4H, m), 6.91(1H, s), 7.20(2H, d, J=8.7 Hz), 7.36(1H, brs), 7.68(1H, brs), 7.71(1H, dd, J=2.7,8.8 Hz), 8.16(1H, d, J=2.7 Hz)

Example 262



(E0262)

E0262 was prepared in a similar manner to that of E0257.

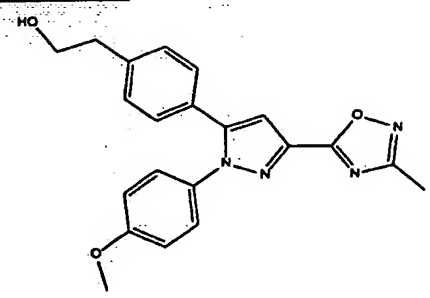
mp. 168-169℃

IR (KBr) : 3381, 3192, 1705, 1695, 1674, 1643, 1614, 1564, 1549, 1516cm-1

Mass (ESI+) : 392 (M+H)+

400MHz 1H NMR (DMSO-d6, d) : 3.79(3H, s), 4.43(2H, s), 6.93(2H, d, J=8.9 Hz), 7.00(2H, d, J=9.0 Hz), 7.08(1H, s), 7.21(2H, d, J=8.9 Hz), 7.28(2H, d, J=9.0 Hz), 7.40(1H, brs), 7.54(1H, brs)

Example 263



(E0263)

A mixture of E0257 (433.5mg) and N,N-dimethylacetamide dimethyl acetal 856mg in toluene 5ml was heated at 100℃ for 40minutes. The reaction mixture was concentrated in vacuo. To the residue was added toluene and concentrated in vacuo. The residue was dissolved in toluene 5ml, hydroxylamine hydrochloride 893mg and AcOH 3ml was added and the mixture was heated at 100℃ for 1hour. The mixture was cooled to

ambient temperature, and partitioned between AcOEt and H2O, The organic layer was washed with H2O, saturated aqueous sodium bicarbonate solution, and saturated aqueous sodium chloride solution, dried over magnesium sulfate, and concentrated in vacuo. The residue was purified by silica gel column chromatography eluted with AcOEt / n-hexane = 40%, 60%, 80%. The pure fraction was collected and concentrated in vacuo. The residue was crystallized from AcOEt / n-hexane to give E0263 (203mg) as a white powder.

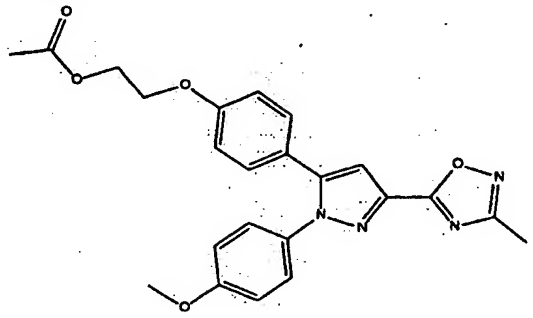
mp. 148-150℃

IR (KBr) : 3431, 3425, 3406, 1614, 1547, 1510cm-1

Mass (ESI+) : 377 (M+H)+

200MHz 1H NMR (DMSO-d6, d) : 2.44(3H, s), 2.72(2H, t, J=6.9 Hz), 3.55-3.65(2H, m), 3.80(3H, s), 4.66(1H, t, J=5.1 Hz), 7.02(2H, d, J=8.9 Hz), 7.20(2H, d, J=9.0 Hz), 7.24(2H, d, J=9.0 Hz), 7.28-7.36(3H, m)

Example 264



(E0264)

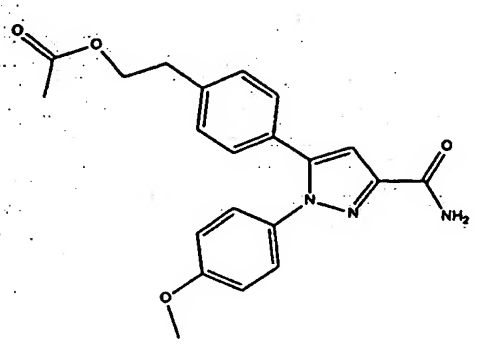
E0264 was prepared in a similar manner to that of E0263.

oil

Mass (ESI+) : 435 (M+H)+

200MHz 1H NMR (DMSO-d6, d) : 2.03(3H, s), 2.44(3H, s), 3.80(3H, s), 4.17-4.22(2H, m), 4.25-4.35(2H, m), 6.97(2H, d, J=8.7 Hz), 7.02(2H, d, J=9.0 Hz), 7.23(2H, d, J=8.7 Hz), 7.27(1H, s), 7.31(2H, d, J=9.0 Hz)

Example 265



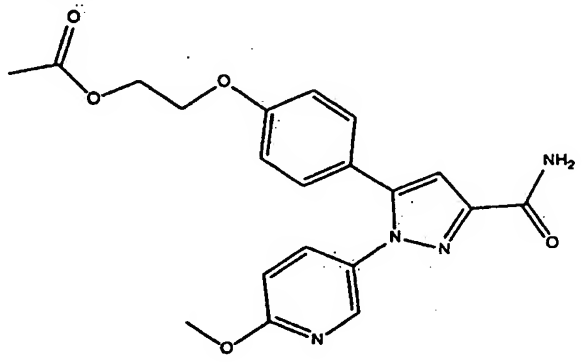
(E0265)

Acetic anhydride 124mg was added to a solution of E0257 (102.6mg) and pyridine 241mg in CH2Cl2 1ml. The reaction mixture was stirred at ambient temperature for 1hour. Acetic anhydride 62mg and pyridine 1ml was added and stirred at ambient overnight. Acetic anhydride 62mg was added and stirred at ambient for 4hours. The mixture was concentrated in vacuo, and the residue was partitioned between ethyl acetate and 1M HCl. The organic layer was washed with saturated aqueous sodium bicarbonate solution and saturated aqueous sodium chloride solution, dried over magnesium sulfate, and concentrated in vacuo. The residual solid was collected and washed with diisopropyl ether to give E0265 (76.3mg) as a white powder.

Mass (ESI+) : 380 (M+H)+

200MHz 1H NMR (DMSO-d6, d) : 1.96(3H, s), 2.87(2H, t, J=6.8 Hz), 3.78(3H, s), 4.20(2H, t, J=6.8 Hz), 6.94(1H, s), 6.98(2H, d, J=8.9 Hz), 7.15-7.30(6H, m), 7.33(1H, s), 7.64(1H, s)

Example 266



(E0266)

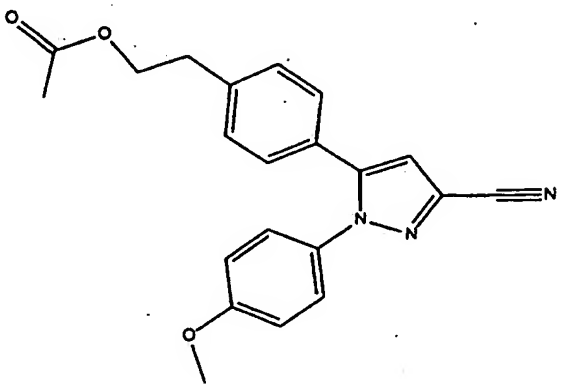
E0266 was prepared in a similar manner to that of E0265.

white powder

Mass (ESI+) : 397 (M+H)+

200MHz 1H NMR (DMSO-d6, d) : 2.03(3H, s), 3.87(3H, s), 4.16-4.21(2H, m), 4.29-4.34(2H, m), 6.88-6.98(4H, m), 7.21(2H, d, J=8.7 Hz), 7.37(1H, brs), 7.68-7.70(1H, brs,overlapping), 7.71(1H, dd, J=2.7,8.8 Hz), 8.16(1H, d, J=2.7 Hz)

Example 267



(E0267)

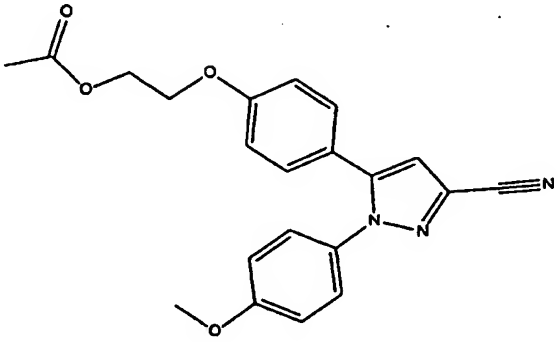
Phosphorus oxychloride 40.4mg was added to DMF 0.5ml under ice bath cooling. After stirring at same temperature for 5 minutes, E0265 (50mg) was added in one portion. The reaction mixture was stirred at same temperature for 1hour, and quenched by adding aqueous sodium bicarbonate solution. The mixture was extracted with ethyl acetate. The organic layer was washed with H2O, saturated aqueous sodium chloride solution, dried over magnesium sulfate, and concentrated in vacuo to give E0267 (45.0mg) as an oil.

Mass (ESI+) : 403 (M+CH3CN+H)+

Mass (API-ES positive) : 362 (M+H)+ , 384 (M+Na)+

200MHz 1H NMR (DMSO-d6, d) : 1.96(3H, s), 2.88(2H, t, J=6.8 Hz), 3.79(3H, s), 4.20(2H, t, J=6.8 Hz), 7.00(2H, d, J=8.9 Hz), 7.15-7.31(6H, m), 7.36(1H, s)

Example 268



(E0268)

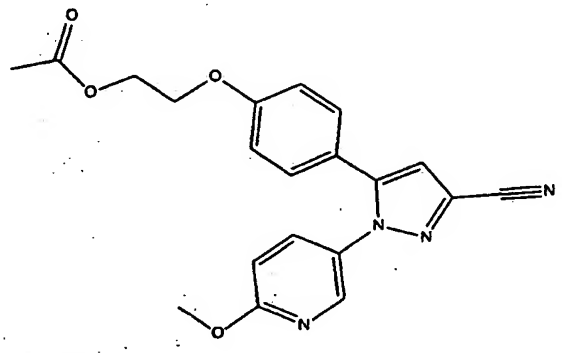
E0268 was prepared in a similar manner to that of E0267.

oil

Mass (ESI+) : 378 (M+H)+

200MHz 1H NMR (DMSO-d6, d) : 2.02(3H, s), 3.79(3H, s), 4.15-4.21(2H, m), 4.29-4.34(2H, m), 6.93-7.04(4H, m), 7.18(2H, d, J=8.8 Hz), 7.24-7.31(3H, m)

Example 269



(E0269)

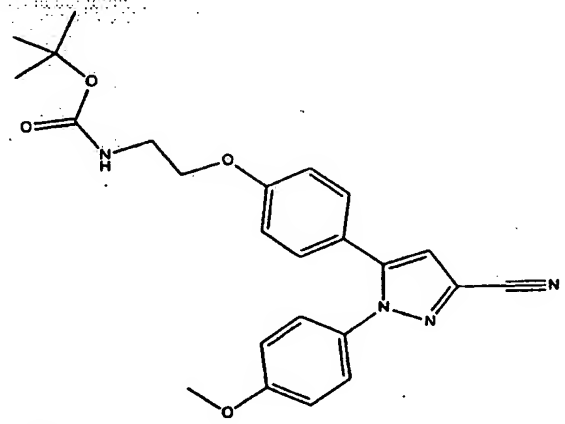
E0269 was prepared in a similar manner to that of E0267.

oil

Mass (ESI+) : 379 (M+H)+

200MHz 1H NMR (DMSO-d6, d) : 2.02(3H, s), 3.88(3H, s), 4.17-4.21(2H, m), 4.29-4.34(2H, m), 6.90-7.03(3H, m), 7.22(2H, d, J=8.8 Hz), 7.36(1H, s), 7.74(1H, dd, J=2.7,8.9 Hz), 8.20(1H, d, J=2.7 Hz)

Example 270



(E0270)

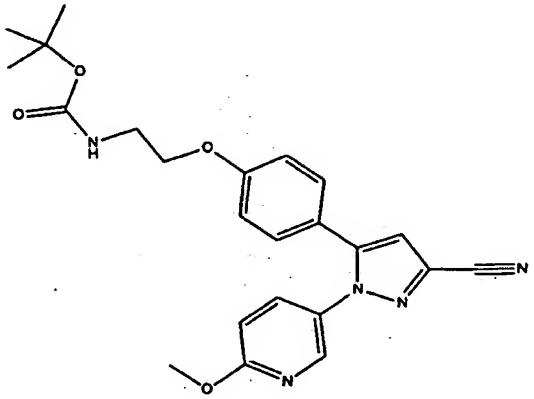
E0270 was prepared in a similar manner to that of E0267.

amorphous powder

Mass (ESI+) : 435 (M+H)+

200MHz 1H NMR (DMSO-d6, d) :1.37(9H, s), 3.22-3.32(2H, m), 3.79(3H, s), 3.92-3.98(2H, m), 6.90-7.08(1H, br,overlapping), 6.92(2H, d, J=8.8 Hz), 7.00(2H, d, J=9.0 Hz), 7.16(2H, d, J=8.8 Hz), 7.28(2H, d, J=9.0 Hz), 7.30(1H, s)

Example 271



(E0271)

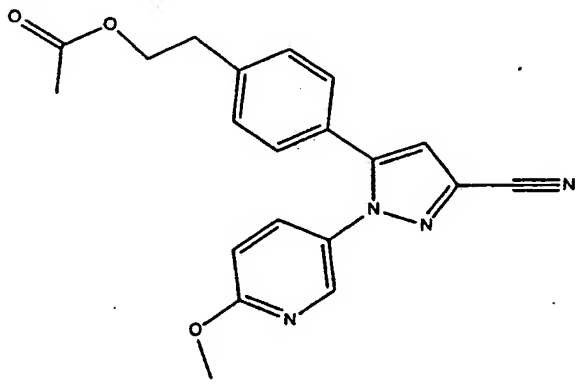
E0271 was prepared in a similar manner to that of E0267.

white powder

Mass (ESI+) : 436 (M+H)+

200MHz 1H NMR (DMSO-d6, d) : 1.37(9H, s), 3.22-3.32(2H, m), 3.88(3H, s), 3.93-3.99(2H, m), 6.90-7.01(1H, overlapping), 6.92(1H, d, J=8.8 Hz), 6.95(2H, d, J=8.8 Hz), 7.21(2H, d, J=8.8 Hz), 7.34(1H, s), 7.73(1H, d, J=2.7,8.8 Hz), 8.20(1H, d, J=2.7 Hz)

Example 272



(E0272)

E0272 was prepared from E0256 in a similar manner to that of E0267.

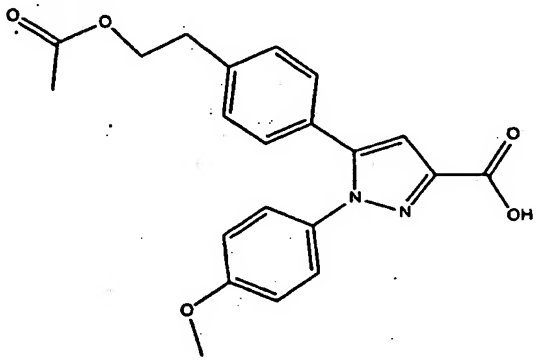
oil

Mass (ESI+) : 363 (M+H)+

200MHz 1H NMR (DMSO-d6, d) :

1.96(3H, s), 2.89(2H, t, J=6.8 Hz), 3.88(3H, s), 4.21(2H, t, J=6.8 Hz), 6.92(1H, d, J=8.8 Hz), 7.22(2H, d, J=8.3 Hz), 7.30(2H, d, J=8.3 Hz), 7.41(1H, s), 7.75(1H, dd, J=8.8,2.7 Hz), 8.20(1H, d, J=2.7 Hz)

Example 273



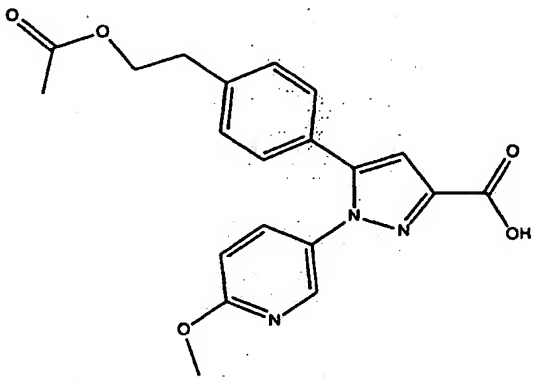
(E0273)

A solution of acetyl chloride 0.28ml in was added to a solution of E0166 (441.6mg) in CH2Cl2 4ml and pyridine 2ml under ice bath cooling. The reaction mixture was stirred at ambient temperature for 1hour. Acetyl chloride 0.14ml was added and stirred at ambient temperature for 1hour. The reaction was quenched by adding aqueous sodium bicarbonate solution and the mixture was stirred at ambient temperature overnight. The mixture was acidified to pH 2 by 6M HCl and extracted with ethyl acetate. The organic layer was washed with H2O and saturated aqueous sodium chloride solution, dried over magnesium sulfate, and concentrated in vacuo. The residue was crystallized from diisopropyl ether to give E0273 (405.3mg) as a white powder.

Mass (ESI+) : 381(M+H)+

200MHz 1H NMR (DMSO-d6, d) : 1.96(3H, s), 2.87(2H, t, J=6.8 Hz), 3.79(3H, s), 4.20(2H, t, J=6.8 Hz), 6.96-7.02(3H, m), 7.15-7.27(6H, m), 12.91(1H, br)

Example 274



(E0274)

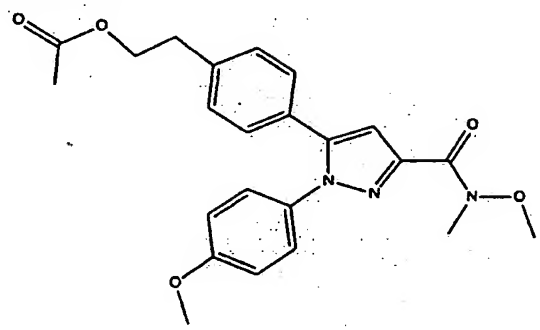
E0274 was prepared in a similar manner to that of E0273.

oil

Mass (ESI+) : 382 (M+H)+

200MHz 1H NMR (DMSO-d6, d) : 2.04(3H, s), 2.94(2H, t, J=7.0 Hz), 3.95(3H, s), 4.29(2H, t, J=7.0 Hz), 6.76(1H, d, J=8.8 Hz), 7.08(1H, s), 7.04-7.35(4H, m), 7.59(1H, dd, J=2.7,8.8 Hz), 8.12(1H, d, J=2.7 Hz)

Example 275



(E0275)

Oxalyl chloride 264mg was added to a suspension of E0273 (395mg) in CH2Cl2 5ml under ice bath cooling. DMF 1drop was added and the mixture was stirred at ambient temperature for 1hour.

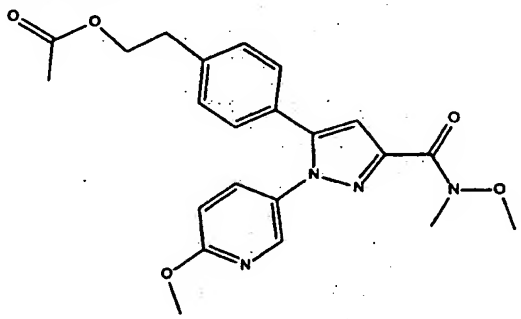
The mixture was concentrated in vacuo. To the residue was added toluene, and concentrated in vacuo. The residue was dissolved in CH2Cl2 30ml, cooled in an ice bath, N,O-dimethylhydroxylamine hydrochloride 203mg and triethylamine 525mg were added and the mixture was stirred at ambient temperature overnight. The mixture was diluted with AcOEt, washed successively with 1M HCl, aqueous sodium bicarbonate solution, and saturated aqueous sodium chloride solution, dried over magnesium sulfate, and concentrated in vacuo. The residue was purified by silica gel column

chromatography eluted with CHCl3, then AcOEt / CHCl3= 10%, 20% to give E0275 (418.4mg) as an oil.

Mass (ESI+) : 424 (M+H)+

200MHz 1H NMR (DMSO-d6, d) : 1.97(3H, s), 2.88(2H, t, J=6.8 Hz), 3.38(3H, s), 3.77(3H, s), 3.78(3H, s), 4.20(2H, t, J=6.8 Hz), 6.94-7.03(3H, m), 7.16-7.27(6H, m)

Example 276



(E0276)

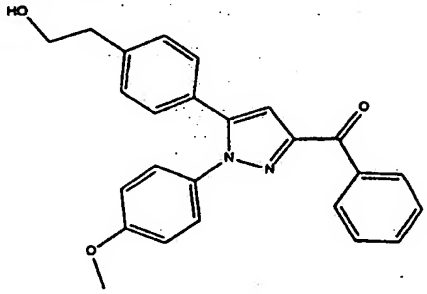
E0276 was prepared from E0274 and N,O-dimethylhydroxylamine hydrochloride in a similar manner to that of E0275.

oil

Mass (ESI+) : 425 (M+H)+

200MHz 1H NMR (DMSO-d6, d) : 1.97(3H, s), 2.89(2H, t, J=6.8 Hz), 3.37(3H, s), 3.77(3H, s), 3.88(3H, s), 4.21(2H, t, J=6.8 Hz), 6.91(1H, d, J=8.8 Hz), 6.98(1H, s), 7.20-7.33(4H, m), 7.70(1H, dd, J=2.8,8.8 Hz), 8.15(1H, d, J=2.8 Hz)

Example 277



(E0277)

To a solution of 1.0M phenylmagnesium bromide in THF 3.4ml was added a solution of E0275 (106.5mg) in THF 2ml under ice bath cooling. After stirring at same temperature for 1hour, the mixture was poured into sat.aqNH4Cl, and extracted with AcOEt. The organic layer was washed with saturated aqueous sodium chloride solution, dried over magnesium sulfate, and concentrated in vacuo. The residue was purified by silica gel

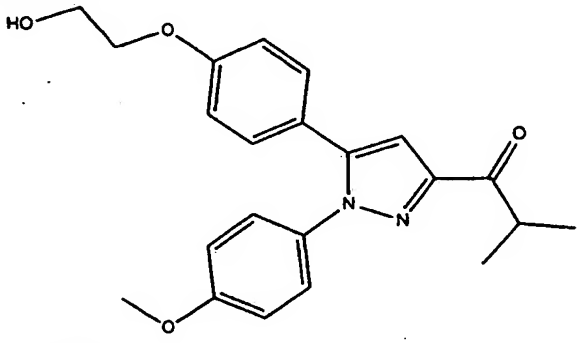
column chromatography eluted with AcOEt / n-hexane = 30%, 40%, 50% to give E0277 (107mg)as an oil.

IR (neat) : 3469, 3435, 3425, 3406, 3398, 3369, 2937, 1647, 1606, 1512cm-1

Mass (ESI+) : 399 (M+H)+

200MHz 1H NMR (DMSO-d6, d) : 2.72(2H, t, J=6.9 Hz), 3.56-3.66(2H, m), 3.80(3H, s), 4.65(1H, t, J=5.1 Hz), 7.02(2H, d, J=8.9 Hz), 7.20(1H, s), 7.22(4H, s), 7.34(2H, d, J=8.9 Hz), 7.52-7.68(3H, m), 8.25(2H, d, J=8.5 Hz)

Example 278



(E0278)

E0278 was prepared in a similar manner to that of E0277.

white powder

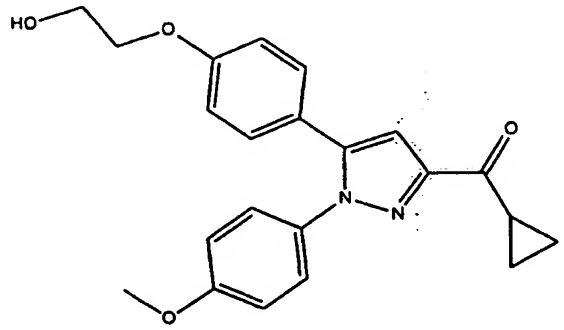
mp. 95-96℃

IR (KBr) : 3498, 3476, 2966, 1678, 1649, 1612, 1547, 1512cm-1

Mass (ESI+) : 381 (M+H)+

200MHz 1H NMR (DMSO-d6, d) : 1.15(6H, d, J=6.8 Hz), 3.61-3.75(3H, m), 3.79(3H, s), 3.95-4.00(2H, m), 4.87(1H, t, J=5.3 Hz), 6.91(2H, d, J=8.7 Hz), 6.98(1H, s), 7.00(2H, d, J=8.9 Hz), 7.17(2H, d, J=8.7 Hz), 7.28(2H, d, J=8.9 Hz)

Example 279



(E0279)

E0279 was prepared in a similar manner to that of E0277.

white powder

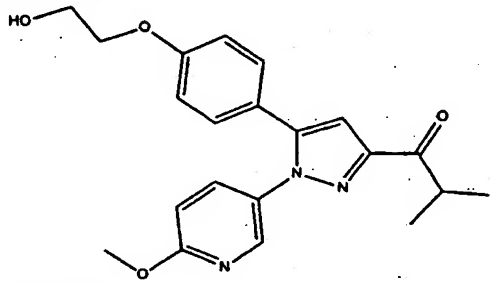
mp.132-133 ℃

IR (KBr) : 3390, 3334, 3288, 1707, 1670, 1612, 1564, 1549, 1512cm-1

Mass (ESI+) : 379 (M+H)+

200MHz 1H NMR (DMSO-d6, d) : 1.04(4H, d, J=6.2 Hz), 3.03(1H, m), 3.65-3.73(2H, m), 3.80(3H, s), 3.95-4.00(2H, m), 4.87(1H, t, J=5.4 Hz), 6.92(2H, d, J=8.7 Hz), 6.96(1H, s), 7.01(2H, d, J=8.9 Hz), 7.18(2H, d, J=8.7 Hz), 7.31(2H, d, J=8.9 Hz)

Example 280



(E0280)

E0280 was prepared in a similar manner to that of E0277.

white powder

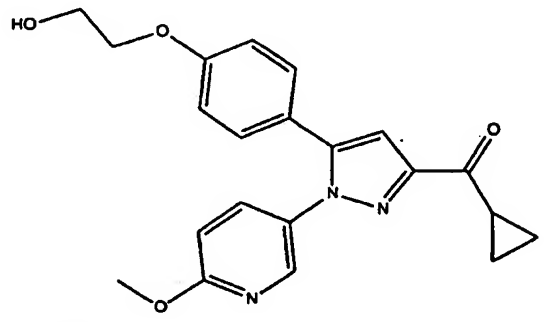
mp. 108-109℃

IR (KBr) : 3440, 2966, 1678, 1610, 1566, 1549, 1533, 1502cm-1

Mass (ESI+) : 382 (M+H)+

200MHz 1H NMR (DMSO-d6, d) : 1.16(6H, d, J=6.9 Hz), 3.64-3.74(3H, m), 3.88(3H, s), 3.96-4.02(2H, m), 4.87(1H, t, J=5.4 Hz), 6.93(1H, d, J=8.9 Hz), 6.94(2H, d, J=8.7 Hz), 7.02(1H, s), 7.21(2H, d, J=8.7 Hz), 7.74(1H, dd, J=2.7,8.9 Hz), 8.18(1H, d, J=2.7 Hz)

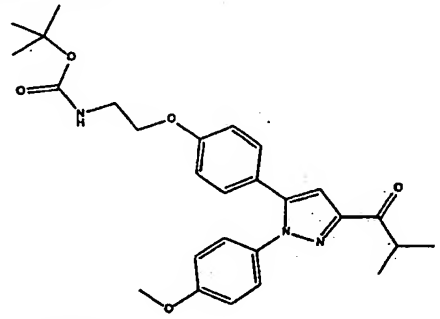
Example 281



(E0281)

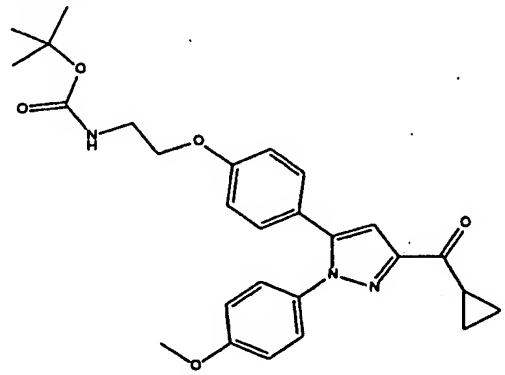
E0281 was prepared in a similar manner to that of E0279.
white powder
mp. 104-106℃
IR (KBr) : 3367, 2947, 1668, 1610, 1566, 1549, 1531cm-1
Mass (ESI+) : 380 (M+H)+
2500MHz 1H NMR (DMSO-d6, d) : 1.05(4H, d, J=6.2 Hz), 3.04(1H, m), 3.65-3.73(2H, m), 3.89(3H, s), 3.96-4.02(2H, m), 4.87(1H, t, J=5.4 Hz), 6.93(1H, d, J=8.8 Hz), 6.95(2H, d, J=8.8 Hz), 7.06(1H, s), 7.22(2H, d, J=8.8 Hz), 7.76(1H, dd, J=2.6,8.8 Hz), 8.21(1H, d, J=2.6 Hz)

Example 282



(E0282)
E0282 was prepared in a similar manner to that of E0277.
white powder
Mass (ESI+) : 480 (M+H)+
200MHz 1H NMR (DMSO-d6, d) : 1.15(6H, d, J=6.9 Hz), 1.37(9H, s), 3.25-3.33(2H, m), 3.68(1H, m), 3.79(3H, s), 3.91-3.98(2H, m), 6.90(2H, d, J=8.7 Hz), 6.90-7.05(1H, overlapping), 6.97(1H, s), 7.00(2H, d, J=8.9 Hz), 7.17(2H, d, J=8.7 Hz), 7.28(2H, d, J=8.9 Hz)

Example 283



(E0283)

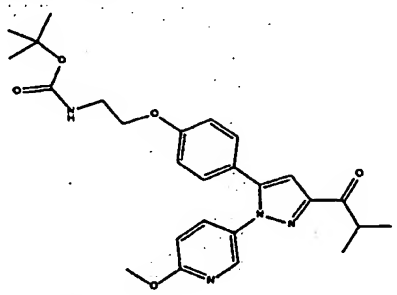
E0283 was prepared in a similar manner to that of E0279.

white powder

Mass (ESI+): 477 (M+H)+

200MHz 1H NMR (DMSO-d6, d) : 1.04(4H, d, J=6.2 Hz), 1.37(9H, s), 3.04(1H, m), 3.22-3.33(2H, m), 3.80(3H, s), 3.95(2H, t, J=5.7 Hz), 6.88-7.03(1H, overlapping), 6.91(2H, d, J=8.7 Hz), 6.97(1H, s), 7.01(2H, d, J=8.9 Hz), 7.18(2H, d, J=8.7 Hz), 7.31(2H, d, J=8.9 Hz)

Example 284



(E0284)

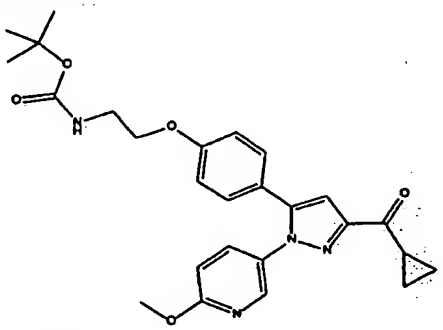
E0284 was prepared in a similar manner to that of E0277.

white powder

Mass (ESI+) : 481 (M+H)+

200MHz 1H NMR (DMSO-d6, d) : 1.16(6H, d, J=6.9 Hz), 1.37(9H, s), 3.22-3.32(2H, m), 3.68(1H, m), 3.88(3H, s), 3.93-3.99(2H, m), 6.90-7.02(5H, m), 7.22(2H, d, J=8.7 Hz), 7.73(1H, dd, J=2.7,8.8 Hz), 8.18(1H, d, J=2.7 Hz)

Example 285



(E0285)

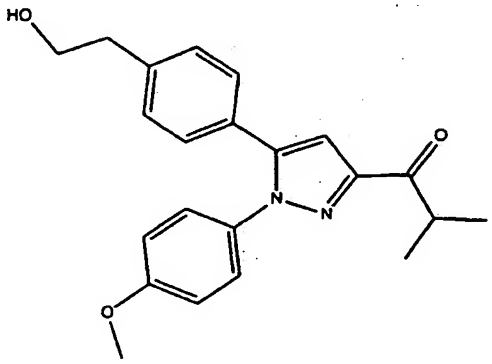
E0285 was prepared in a similar manner to that of E0279.

white powder

Mass (ESI+): 479 (M+H)+

200MHz 1H NMR (DMSO-d6, d) : 1.05(4H, d, J=6.2 Hz), 1.37(9H, s), 3.04(1H, m), 3.23-3.33(2H, m), 3.89(3H, s), 3.93-3.99(2H, m), 6.89-7.08(5H, m), 7.22(2H, d, J=8.7 Hz), 7.76(1H, dd, J=2.7,8.8 Hz), 8.21(1H, d, J=2.7 Hz)

Example 286



(E0286)

E0286 was prepared from E0275 in a similar manner to that of E0277.

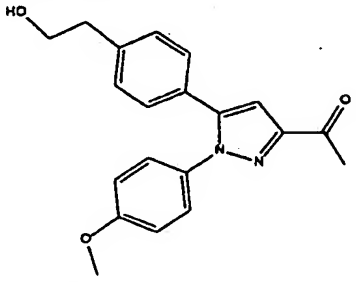
oil

IR (neat) : 3487, 3469, 3435, 3408, 3398, 3369, 2966, 2933, 1678, 1512cm-1

Mass (ESI+) : 365 (M+H)+

200MHz 1H NMR (DMSO-d6, d) : 1.19(6H, d, J=7.9 Hz), 2.70(2H, t, J=6.9 Hz), 3.54-3.75(3H, m), 3.79(3H, s), 4.64(1H, t, J=5.1 Hz), 7.00(2H, d, J=8.9 Hz), 7.02(1H, s), 7.16(2H, d, J=8.6 Hz), 7.21(2H, d, J=8.6 Hz), 7.29(2H, d, J=8.9 Hz)

Example 287



(E0287)

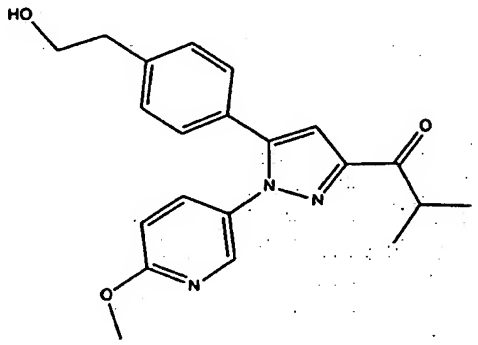
To a solution of 1.0M methylmagnesium bromide in diethyl ether 2.8ml was added a solution of E0275 (237.6mg) in THF 4ml dropwise under ice bath cooling. After stirring at same temperature for 30minues the mixture was poured into sat.aqNH4Cl, and extracted with AcOEt. The organic layer was washed successively with a mixture of 1M HCl and saturated aqueous sodium chloride solution, saturated aqueous sodium bicarbonate solution, and saturated aqueous sodium chloride solution, dried over

magnesium sulfate, and concentrated in vacuo.The residue was dissolved in THF1ml, 1M NaOH 0.4ml was added and the mixture was stirred at ambient temperature for several hours. The mixture was neutralized with 1M HCl 0.4ml, and partitioned between AcOEt and saturated aqueous sodium chloride solution. The organic layer was dried over magnesium sulfate, and concentrated in vacuo. The residue was purified by silica gel column chromatography eluted with AcOEt / n-hexane = 50% to give E0287 (139.1mg) as a white powder.

Mass (ESI+) : 337 (M+H)+

200MHz 1H NMR (DMSO-d6, d) : 2.54(3H, s), 2.70(2H, t, J=6.9 Hz), 3.55-3.64(2H, m), 3.80(3H, s), 4.65(1H, t, J=5.1 Hz), 7.00(2H, d, J=8.9 Hz), 7.01(1H, s), 7.15(2H, d, J=8.5 Hz), 7.21(2H, d, J=8.5 Hz), 7.29(2H, d, J=8.9 Hz)

Example 288



(E0288)

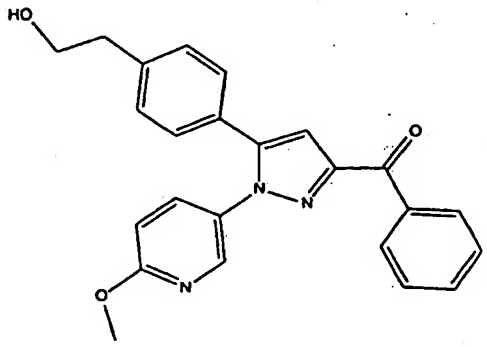
E0288 was prepared in a similar manner to that of E0287.

oil

Mass (ESI+) : 366 (M+H)+

200MHz 1H NMR (DMSO-d6, d) : 1.16(6H, d, J=6.9 Hz), 2.72(2H, t, J=6.9 Hz), 3.55-3.75(3H, m), 3.88(3H, s), 4.65(1H, t, J=5.1 Hz), 6.93(1H, d, J=8.8 Hz), 7.05(1H, s), 7.17-7.29(4H, m), 7.76(1H, dd, J=8.8,2.7 Hz), 8.19(1H, d, J=2.7 Hz)

Example 289



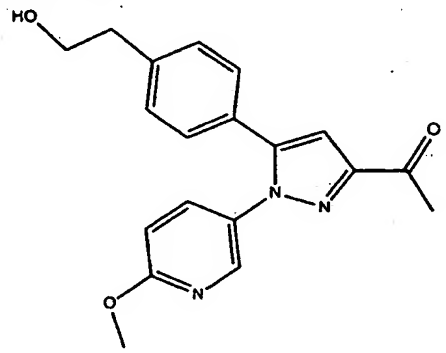
(E0289)

E0289 was prepared in a similar manner to that of E0287.

oil

200MHz 1H NMR (DMSO-d6, d) : 2.73(2H, t, J=6.9 Hz), 3.57-3.66(2H, m), 3.89(3H, s), 4.66(1H, t, J=5.0 Hz), 6.94(1H, d, J=8.8 Hz), 7.23(1H, s), 7.15-7.35(4H, m), 7.52-7.72(3H, m), 7.80(1H, dd, J=2.7,8.8 Hz), 8.23-8.32(3H, m)

Example 290



(E0290)

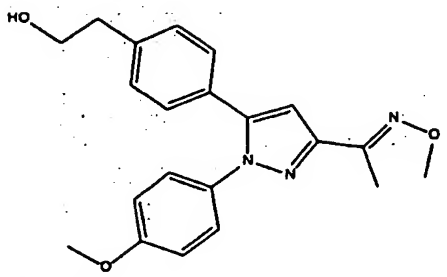
E0290 was prepared in a similar manner to that of E0287.

white powder

Mass (ESI+) : 338 (M+H)+

00MHz 1H NMR (DMSO-d6, d) : 2.55(3H, s), 2.71(2H, t, J=6.9 Hz), 3.55-3.65(2H, m), 3.89(3H, s), 4.65(1H, t, J=5.1 Hz), 6.93(1H, d, J=8.8 Hz), 7.05(1H, s), 7.19(2H, d, J=8.6 Hz), 7.24(2H, d, J=8.6 Hz), 7.75(1H, dd, J=2.7,8.8 Hz), 8.19(1H, d, J=2.7 Hz)

Example 291



(E0291)

A mixture of E0287 (127mg), O-methylhydroxylamine hydrochloride 47.3mg and pyridine in EtOH 3ml was heated at 60℃ for 1hour. The mixture was concentrated in vacuo and the residue was purified by silica gel column chromatography eluted with AcOEt / n-hexane = 40%. The pure fraction was collected and concentrated in vacuo. The residue was crystallized from diisopropyl ether to give E0291 (103.2mg) as a white powder.

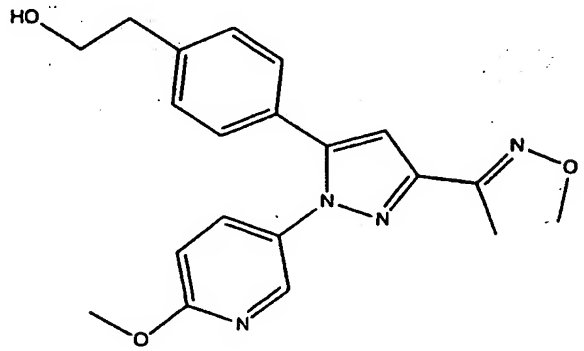
mp. 82-86℃

IR (KBr) : 3359, 3269, 3246, 2939, 1549, 1512cm-1

Mass (ESI+) : 366(M+H)+

200MHz 1H NMR (DMSO-d6, d) : 2.20(3H, s), 2.70(2H, t, J=6.9 Hz), 3.54-3.65(2H, m), 3.78(3H, s), 3.92(3H, s), 4.65(1H, t, J=5.0 Hz), 6.77(1H, s), 6.97(2H, d, J=8.9 Hz), 7.12-7.26(6H, m)

Example 292



(E0292)

E0292 was prepared in a similar manner to that of E0291.

white powder

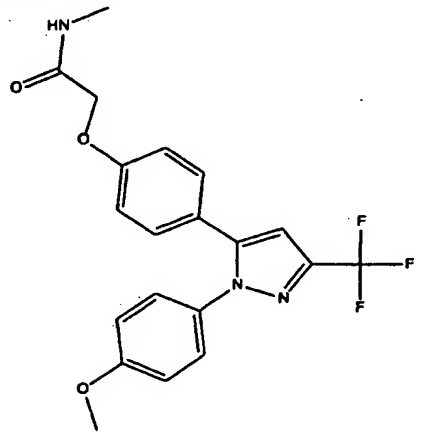
mp.94-95℃

IR (KBr) : 3469, 3433, 3423, 3404, 3400, 3371, 1647, 1549cm-1

Mass (ESI+) : 267(M+H)+

200MHz 1H NMR (DMSO-d6, d) : 2.20(3H, s), 2.71(2H, t, J=6.8 Hz), 3.55-3.65(2H, m), 3.87(3H, s), 3.92(3H, s), 4.65(1H, t, J=5.0 Hz), 6.81(1H, s), 6.90(1H, d, J=8.8 Hz), 7.18(2H, d, J=8.7 Hz), 7.23(2H, d, J=8.7 Hz), 7.69(1H, dd, J=8.8,2.7 Hz), 8.11(1H, d, J=2.7 Hz)

Example 293



(E0293)

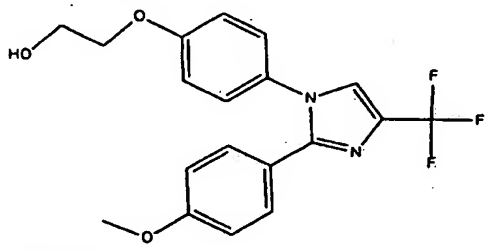
To a solution of E0225 (100 mg) in methanol (21 ml) was added a solution of methyl amine in methanol (40%, 92 ml). After stirring at room temperature overnight, the mixture was evaporated to give oil, which was purified with preparative TLC (1 mm, 60% ethyl acetate / hexane) to give E0293 as an oil (97 mg, 100%).

NMR(CDCl3), 2.92(3H, d, J=5.0 Hz), 3.83(3H, s), 4.49(2H, s), 6.69(1H, s), 6.82-6.91(4H, m), 7.14-7.24(4H, m).

MS(ESI+); 428.2(M+Na).

IR(Neat, 20727-11), 1693.2cm-1.

Example 294



(E0294)

4-[2-(4-methoxyphenyl)-4-trifluoromethyl-1H-imidazol-1-yl]phenol (250 mg), 2-chloroethanol (0.3 ml), potassium carbonate (620 mg) and potassium iodide (745 mg) in N,N-dimethylformamide (1.3 ml) was stirred at 75℃ for 6 hours. Then the

reaction mixture was poured into water and extracted with ethyl acetate, dried over MgSO4 and evaporated in vacuo.The residue was purified by column chromatography silica-gel eluting with (n-Hexane:AcOEt=1:1) to give E0294 (2-{4-[2-(4-methoxyphenyl)-4- (trifluoromethyl)-1H-imidazol-1-yl]-phenoxy}ethanol)(0.14 g).

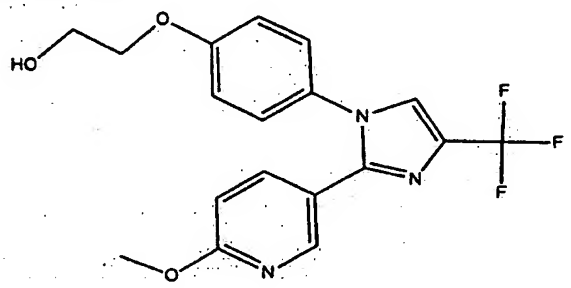
m.p. 149-150℃

NMR (DMSO-d6) d; 3.67-3.74 (2H, m), 3.74 (3H, s), 4.03 (2H, t, J=5.3Hz), 4.91 (1H, t, J=5.1Hz), 6.90 (2H, d, J=9.3Hz, 1.9Hz), 7.03 (2H, d, J=8.9Hz), 7.24-7.33 (4H, m), 8.07 (1H, d, J=1.1Hz).

IR (KBr): 3392, 3298, 3111, 3064, 3024, 2951, 2871, 1693, 1610 cm-1.

Mass m/e : 379 (M++1).

Example 295



(E0295)

2-{4-[2-(2-Methoxypyridin-6-yl)-4-(trifluoromethyl)-1H-imidazol-1-yl]phenoxy}ethanol (E0295) (0.2 g) was obtained from 4-[2-(2-methoxypyridin-6-yl)-4-trifluoromethyl-1H-imidazol-1-yl]phenol (0.21 g) in the similar manner that of example (E0294).

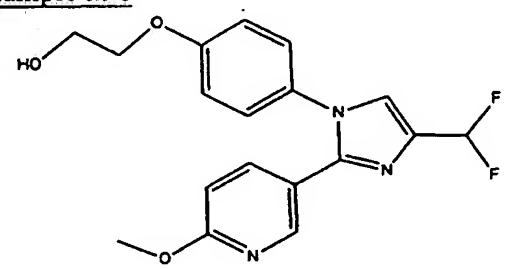
m.p. 89-91℃

NMR (DMSO-d6) d; 3.70-7.36 (2H, m), 3.84 (3H, s), 4.04 (2H, t, J=5.0Hz), 4.91 (1H, t, J=5.3Hz), 6.81 (1H, d, J=8.6Hz), 7.05 (2H, d, J=8.9Hz), 7.34-7.07 (2H, m), 7.65 (1H, dd, J=8.6Hz, 2.4Hz), 8.08 (1H, d, J=2.4Hz), 8.16 (1H, d, J=1.4Hz).

IR (KBr): 3381, 3292, 3221, 3113, 3068, 2954, 2871, 1695, 1685, 1651, 1610 cm-1.

Mass m/e : 380 (M++1).

Example 296



(E0296)

2-{4-[4-(Difluoromethyl)-2-(2-methoxypyridin-6-yl)-1H-imidazol-1-yl]phenoxy}ethanol (E0296) (65 mg) was obtained from 4-[4-difluoromethyl-2-(2-methoxypyridin-6-yl)-1H-imidazol-1-yl]phenol (0.2 g) in the similar manner that of E0294.

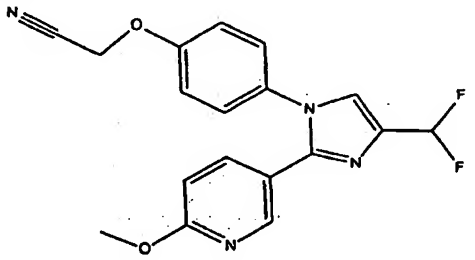
m.p. 72-73℃

NMR (DMSO-d6) d; 3.69-3.72 (2H, m), 3.83 (3H, s), 4.90 (1H, t, J=5.4Hz), 6.80 (1H, d, J=8.6Hz), 7.00 (1H, t, J=54.9Hz), 7.00-7.06 (2H, m), 7.28-7.34 (2H, m), 7.63 (1H, dd, J=8.6Hz, 2.4Hz), 7.81 (1H, t, J=2.1Hz), 8.07 (1H, d, J=2.4Hz).

IR (KBr): 3361, 3116, 3068, 3016, 2956, 2873, 1738, 1697, 1687, 1649, 1612 cm-1.

Mass m/e : 362 (M++1).

Example 297



(E0297)

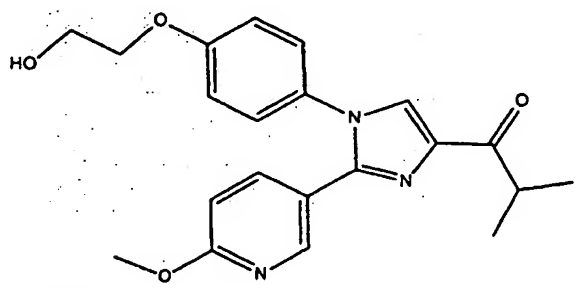
{4-[4-(Difluoromethyl)-2-(2-methoxypyridin-6-yl)-1H-imidazol-1-yl]phenoxy}acetonitrile (E0297) (1 g) was obtained from 4-[4-difluoromethyl-2-(2-methoxypyridin-6-yl) -1H-imidazol-1-yl]phenol (1 g) and chloroacetonitrile (0.4 ml) in the similar manner that of E0294 as an oil.

NMR (DMSO-d6) d; 3.83 (3H, s), 5.25 (2H, s), 6.80 (1H, d, J=8.7Hz), 7.01 (1H, t, J=54.8Hz), 7.18 (2H, dd, J=7.0Hz, 1.9Hz), 7.43 (2H, dd, J=7.0Hz, 1.9Hz), 7.63 (1H, dd, J=8.7Hz, 2.2Hz), 7.86 (1H, t, J=2.1Hz), 8.07 (1H, d, J=2.2Hz).

IR (Neat): 3574, 3431, 3415, 3213, 3157, 3118, 3078, 2960, 2860, 1726, 1660, 1604 cm-1.

Mass m/e : 357 (M++1).

Example 298



(E0298)

E0298 was obtained from P0053 in the similar manner that of E0294.

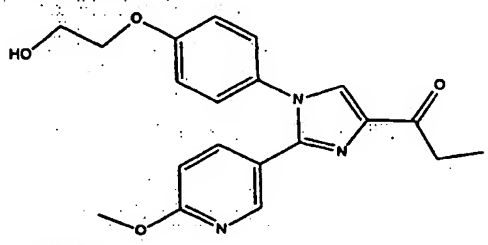
m.p. 1118.2-118.5 ℃

NMR (DMSO-d6) d; 1.14 (6H,d, J=6.8Hz), 3.56-3.66 (1H, m), 3.70-3.77 (2H, m), 3.83 (3H, s), 4.04 (2H, t, J=5.0 Hz), 4.91 (1H, t, J=5.4Hz), 6.82 (1H, d, J=8.7Hz), 7.05 (2H, dd, J=9.4Hz, 2.0Hz), 7.34 (2H, dd, J=9.4Hz, 2.0Hz), 7.66 (1H, dd, J=8.7Hz, 2.3Hz), 8.08 (1H, d, J=2.3Hz), 8.18 (1H, s).

IR (KBr): 3340, 3140, 3070, 2968, 2933, 1664, 1608 cm-1.

Mass m/e : 382 (M++1).

Example 299



(E0299)

E0299 was obtained from P0054 in the similar manner that of E0294.

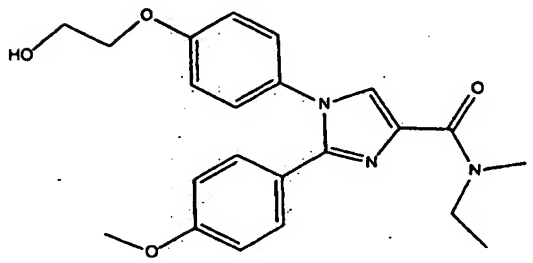
m.p. 100-104 ℃

NMR (DMSO-d6) d; 1.10 (3H, t, J=7.4Hz), 2.96 (2H, q, J=7.4Hz), 3.73 (2H, q, J=4.8Hz), 3.84 (3H, s), 3.98 -4.08 (2H, m), 4.91 (1H, t, J=5.4Hz), 6.81 (1H, d, J=8.6Hz), 7.04 (2H, dt, J=9.6Hz, 2.8Hz), 7.32 (2H, dt, J=9.6Hz, 2.8Hz), 7.65 (1H, dd, J=8.6 hz, 2.4Hz), 8.08 (1H, d, J=2.4Hz), 8.17 (1H, s).

IR (KBr): 3332, 3138, 2976, 2935, 1672, 1610 cm-1.

Mass m/e : 368 (M++1).

Example 300



(E0300)

E0300 was obtained in the similar manner that of E0294.

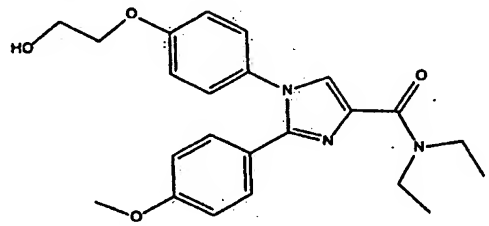
m.p. 124-126 ℃

NMR (DMSO-d6) d; 1.08-1.28 (3H, m), 2.90-3.02 (2H, m), 3.40-3.54 (2H, m), 3.74 (3H, s), 3.69-3.77 (1H, m), 3.98-4.00 (2H, m), 4.03 (2H, t, J=5.0Hz), 4.91 (1H, t, J=5.0Hz), 6.89 (2H, d, J=8.8Hz), 7.02 (2H, d, J=8.9Hz), 7.24-7.29 (4H, m), 7.72 (1H, s).

IR (KBr): 3367, 3126, 3072, 2968, 2933, 2875, 2839, 1604 cm-1.

Mass m/e : 396 (M++1).

Example 301



(E0301)

E0301 was obtained in the similar manner that of E0294.

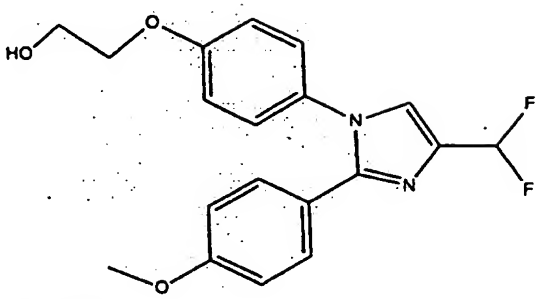
m.p. 141-143 ℃

NMR (DMSO-d6) d; 1.10-1.30 (6H, m), 3.28-3.50 (2H, m), 3.67-3.78 (2H, m), 3.74 (3H, s), 3.80-4.06 (2H, m), 4.03 (2H, t, J=4.9Hz), 4.91 (1H, t, J=9.2 Hz), 6.90 (2H, d, J=8.8Hz), 7.02 (2H, d, J=8.8Hz), 7.26 (4H, d, J=8.8Hz), 7.71 (1H, s).

IR (KBr): 3398, 3365, 3224, 3126, 2970, 2931, 2875, 1601 cm-1.

Mass m/e : 410 (M++1).

Example 302



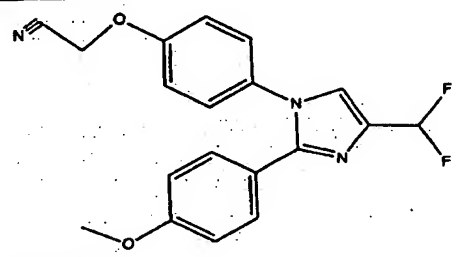
(E0302)

E0302 was obtained according to a similar manner to that of E0294.

1H NMR (CDCl3, ppm) d 3.78(3H, s), 3.92-4.05(2H, m), 4.05-4.18(2H, m), 6.77(1H, d, J=111.66 Hz), 6.72-6.85(2H, m), 6.89-7.00(2H, m), 7.09-7.22(2H, m), 7.27-7.40(3H, m),

MS (ESI, m/e) 361(M+1)

Example 303



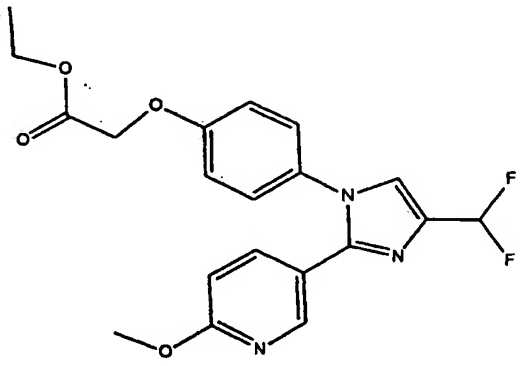
(E0303)

E0303 was obtained according to a similar manner to that of E0294.

1H NMR (CDCl3, ppm) d 3.79(3H, s), 4.82(2H, s), 6.73-6.88(2H, m), 6.95-7.09(2H, m), 7.18-7.39(5H, m),

MS (ESI, m/e) 356(M+1)

Example 304



(E0304)

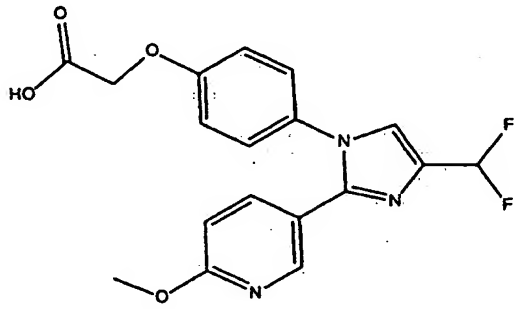
2-{4-[2-(4-methoxyphenyl)-4-(trifluoromethyl)-1H-imidazol-1-yl]phenoxy}ethanol (300 mg) and sodium hydride (60% in oil) (42 mg) in N,N-dimethylformamide (3 ml) was stirred at room temperature for 30 minutes. Then ethylbromoacetate (115 ml) was added and stirred at room temperature for 1 hour. Then the reaction mixture was poured into water and extracted with ethyl acetate, dried over MgSO4 and evaporated in vacuo.The residue was purified by column chromatography silica-gel eluting with (n-Hexane:AcOEt=2:1) to give ethyl {4-[4-(difluoromethyl)-2-(2-methoxypyridin-6-yl)-1H-imidazol-1-yl]phenoxy}acetate (E0304) (0.36 g) as an oil.

NMR (DMSO-d6) d; 1.21 (3H, t, J=7.1Hz), 3.83 (3H, s), 4.17 (2H, q, J=7.1Hz), 4.86 (2H, s), 6.79 (1H, d, J=8.6Hz), 7.00 (1H, t, J=54.9Hz), 7.04 (2H, dd, J=6.9Hz, 2.2Hz), 7.33 (2H, dd, J=6.9Hz, 2.2Hz), 7.64 (1H, dd, J=8.6Hz, 2.4Hz), 7.82 (1H, t, J=2.3Hz), 8.05 (1H, d, J=2.4Hz).

IR (Neat): 3448, 3153, 3114, 3076, 2983, 2951, 1755, 1738, 1608 cm-1.

Mass m/e : 404 (M++1).

Example 305



(E0305)

1N aqueous sodium hydroxide (0.79 ml) was added to a solution of E0304 (160 mg) in ethanol (2 ml). After stirring at room temperature for 1 hour, the reaction mixture was poured into water and ethyl acetate, and extracted with water. Then the water layer was acidified with 10% aqueous potassium hydrogen sulfate, extracted with ethyl acetate, dried over MgSO4 and evaporated in vacuo. The resulting precipitates were collected by filtration and washed with diisopropyl ether to give E0305 (126 mg).

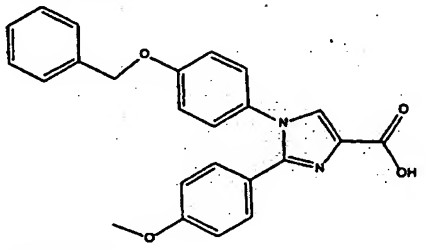
m.p. 122-124℃

NMR (DMSO-d6) d; 3.83 (3H, s), 4.75 (2H, s), 6.80 (1H, d, J=8.8Hz), 7.00 (1H, t, J=54.8Hz), 7.00-7.06 (2H, m), 7.32 (2H, dd, J=9.6Hz, 3.2Hz), 7.63 (1H, dd, J=8.8Hz, 2.4Hz), 7.82 (1H, t, J=2.1Hz), 8.07 (1H, d, J=2.4Hz), 13.09 (1H, br).

IR (KBr): 3465, 3446, 3122, 3066, 3010, 2966, 2522, 1738, 1651, 1612 cm-1.

Mass m/e : 376 (M++1).

Example 306



(E0306)

E0306 was obtained in the similar manner that of E0305.

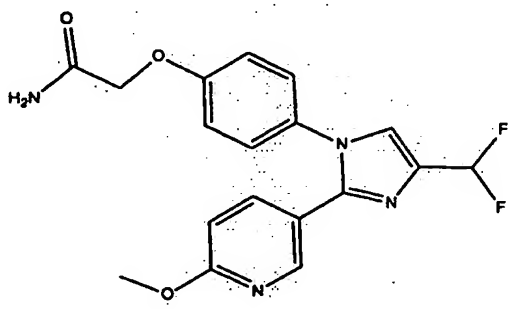
m.p. 113-115℃

NMR (DMSO-d6) d; 3.75 (3H, s), 5.15 (2H, s), 6.88 (2H, d, J=8.8Hz), 7.10 (2H, d, J=8.9Hz), 7.24-7.45 (9H, m), 7.96 (1H, s) 11.0-12.5 (1H, br).

IR (KBr): 3392, 3224, 3145, 3076, 2972, 2935, 2893, 1701, 1610 cm-1.

Mass m/e : 401 (M++1).

Example 307



(E0307)

A mixture of ethyl E0304 (210 mg) and sodium methoxide (84 mg) in formamide (3 ml) was stirred at 100℃ for 1 hour. After cooling to room temperature, the reaction mixture was poured into water and extracted with ethyl acetate, dried over MgSO4 and evaporated in vacuo. The resulting precipitates were collected by filtration and washed with diisopropyl ether to give E0307 (144 mg).

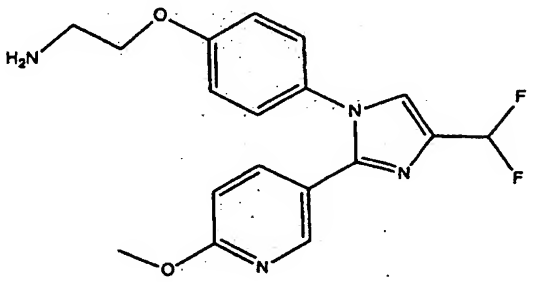
m.p. 140-141℃

NMR (DMSO-d6) d; 3.83 (3H, s), 4.49 (2H, s), 6.80 (1H, d, J=8.5Hz), 7.00 (1H, t, J=54.9Hz),7.05 (2H, dd, J=6.9Hz, 2.0Hz), 7.35 (2H, dd, J=9.5Hz, 2.0Hz), 7.43 (1H, s), 7.61 (1H, s), 7.63 (1H, dd, J=8.6Hz, 2.4Hz), 7.81 (1H, t, J=2.0Hz), 8.07 (1H, d, J=2.4Hz).

IR (KBr): 3467, 3284, 3170, 3107, 2956, 1684, 1645, 1610 cm-1.

Mass m/e : 375 (M++1).

Example 308



(E0308)

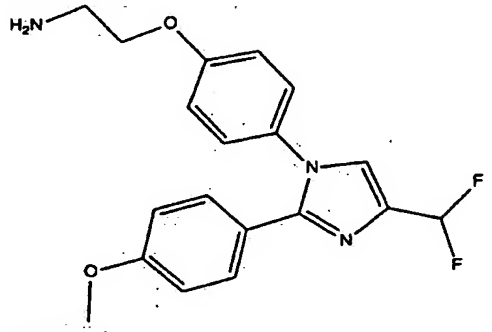
Lithium aluminium hydride (13 mg) was added to a solution of E0297 (83 mg) in tetrahydrofuran (2 ml). After stirring at room temperature for 1 hour, the reaction mixture was poured into saturated aqueous ammonium chloride and extracted with ethyl acetate, dried over MgSO4 and evaporated in vacuo. to give E0308 (67 mg) as an oil.

NMR (DMSO-d6) d; 2.88 (2H, t, J=5.7Hz), 3.78 (2H, s), 3.83 (3H, s), 3.96 (2H, t, J=5.7Hz), 6.80 (1H, d, J=8.7Hz), 6.82 (1H, t, J=54.1Hz), 6.99-7.06 (2H, m), 7.28-7.34 (2H, m), 7.63 (1H, dd, J=8.7Hz, 2.4Hz), 7.80 (1H, t, J=2.0Hz), 8.07 (1H, d, J=2.4Hz).

IR (Neat): 3359, 3276, 3219, 3157, 3113, 3082, 3016, 2954, 2881, 1653, 1610 cm-1.

Mass m/e : 361 (M++1).

Example 309

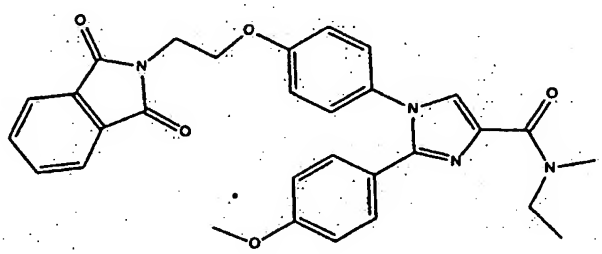


(E0309)

E0309 was obtained according to a similar manner to that of E0308.

MS (ESI, m/e) 360(M+1)

Example 310



(E0310)

A mixture of E0300 (0.22 g), phthalimide (128 mg), triphenylphosphine (219 mg) and diethylazocarboxylate (131 ml) in tetrahydrofuran (2 ml) was stirred at room temperature for 2 hours. The reaction mixture was poured into water and extracted with ethyl acetate, dried over MgSO4 and evaporated in vacuo. The residue was purified by column chromatography silica-gel eluting with (n-Hexane:AcOEt=1:1 -> 0:1). The resulting precipitates were corrected by filtration and washed with diisopropyl ether to give E0310 (235 mg).

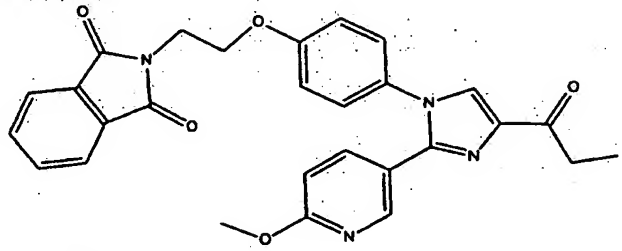
m.p. 135-136℃

NMR (DMSO-d6) d; 1.08-1.28 (3H, m), 2.89-3.02 (2H, m), 3.40-3.50 (2H, m), 3.73 (3H, s), 3.69-3.77 (1H, m), 3.99 (2H, t, J=5.4 Hz), 4.27 (2H, t, J=5.4Hz), 6.87 (2H, d, J=8.8Hz), 6.98 (2H, d, J=8.9Hz), 7.24 (4H, d, J=8.8Hz), 7.68 (1H, s), 7.83-7.93(4H, m).

IR (KBr): 3537, 3431, 3305, 3236, 3143, 2970, 2935, 1716, 1649, 1610 cm-1.

Mass m/e : 525 (M++1).

Example 311



(E0311)

E0311 was obtained in the similar manner that of E0310.

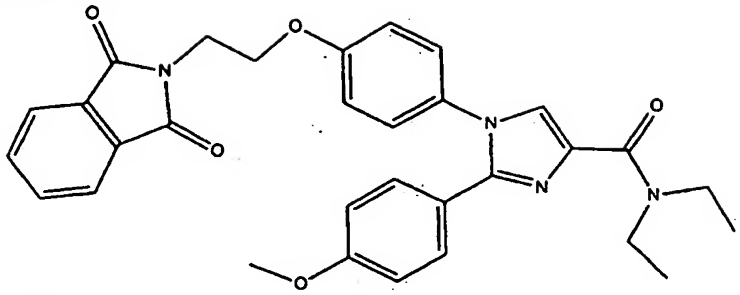
m.p. 155-157 ℃

NMR (DMSO-d6) d; 1.09 (3H, t, J=7.3Hz), 2.95 (2H, q, J=7.3Hz), 3.83 (3H, s), 3.98 (2H, t, J=5.7Hz), 4.27 (2H, t, J=5.7Hz), 6.79 (1H, d, J=8.6Hz), 7.00 (2H, d, J=8.9Hz), 7.30 (2H, d, J=8.8Hz), 7.61 (1H, dd, J=8.6Hz, 2.5Hz), 7.83-7.93 (4H, m), 7.93 (1H, d, J=2.5Hz), 8.13 (1H, s).

IR (KBr): 3207, 3140, 3066, 2970, 2941, 1712, 1674, 1610 cm-1.

Mass m/e : 497 (M++1).

Example 312



(E0312)

E0312 was obtained in the similar manner that of E0310.

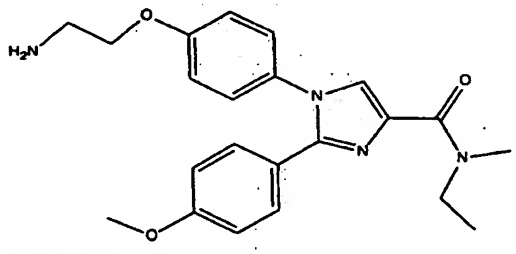
m.p. 109-111 ℃

NMR (DMSO-d6) d; 1.08-1.30 (6H, m), 3.32-3.51 (2H, m), 3.72 (3H, s), 3.80-3.96 (2H, m), 3.99 (2H, t, J=5.9Hz), 4.27 (2H, t, J=5.9 Hz), 6.87 (2H, d, J=8.9Hz), 6.98 (2H, d, J=8.9Hz), 7.24 (4H, d, J=8.8Hz), 7.67 (1H, s), 7.83-7.91 (4H, m).

IR (KBr): 3419, 3215, 3143, 3053, 2970, 2935, 2879, 2841, 1776, 1712, 1608 cm-1.

Mass m/e : 539 (M++1).

Example 313



(E0313)

E0310 (220 mg) and hydrazine hydride (203 ml) in acetonitrile (3 ml) was stirred at reflux condition for 2 hours. After cooling at room temperature, The reaction mixture was poured into 1N aqueous sodium hydroxide and extracted with ethyl acetate, dried over MgSO4 and evaporated in vacuo. The resulting precipitates were corrected by filtration and washed with diisopropyl ether to give E0313 (157 mg).

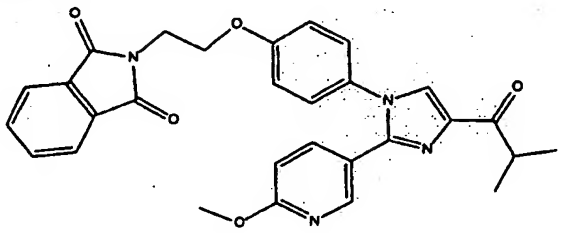
m.p. 134-135℃

NMR (DMSO-d6) d; 1.09-1.30 (3H, m), 1.78 (2H, br), 2.88 (2H. t, J=5.7Hz), 2.89-3.00 (2H, m), 3.40-3.53 (2H, m), 3.74 (3H, s), 3.69-3.77 (1H, m), 3.94 (2H, t, J=5.7 Hz), 6.89 (2H, d, J=8.8Hz), 7.01 (2H, d, J=8.9Hz), 7.26 (4H, d, J=8.8Hz), 7.72 (1H, s).

IR (KBr): 3427, 3377, 3350, 3209, 3105, 3066, 2962, 2935, 2877, 2835, 1606 cm-1.

Mass m/e : 395 (M++1).

Example 314



(E0314)

E0314 was obtained in the similar manner that of E0313.

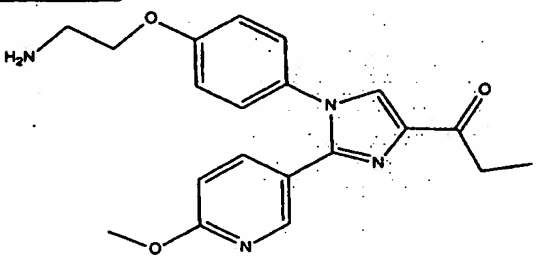
m.p. 118-120 ℃

NMR (DMSO-d6) d; 1.14 (6H,d, J=6.8Hz), 3.56-3.67(1H, m), 3.83 (3H, s), 3.96-4.09 (4H, m), 6.79 (1H, d, J=8.6Hz), 7.00 (2H, d, J=8.9Hz), 7.31 (2H, d, J=8.9Hz), 7.61 (1H, dd, J=8.6Hz, 2.4Hz), 7.85-7.91 (4H, m), 8.08 (1H, d, J=2.4Hz), 8.98 (1H, s).

IR (KBr): 3246, 3141, 3041, 2983, 2935, 2875, 1749, 1707, 1670, 1610 cm-1.

Mass m/e : 511 (M++1).

Example 315



(E0315)

E0315 was obtained in the similar manner that of E0313.

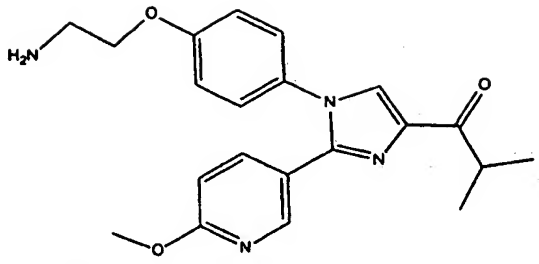
m.p. 112-113 ℃

NMR (DMSO-d6) d; 1.10 (3H, t, J=7.4Hz), 1.59 (2H, br), 2.88 (2H, t, J=5.7Hz), 2.96 (2H, q, J=7.4Hz), 3.84 (3H, s), 3.96 (2H, t, J=5.7Hz), 6.82 (1H, d, J=8.6Hz), 7.02-7.08 (2H, m), 7.28-7.36 (2H, m), 7.66 (1H, dd, J=8.6Hz, 2.4Hz), 8.08 (1H, d, J=2.4Hz), 8.17 (1H, s).

IR (KBr): 3359, 3296, 3138, 3055, 2947, 1670, 1608 cm-1.

Mass m/e : 367 (M++1).

Example 316



(E0316)

E0316 was obtained in the similar manner that of E0313.

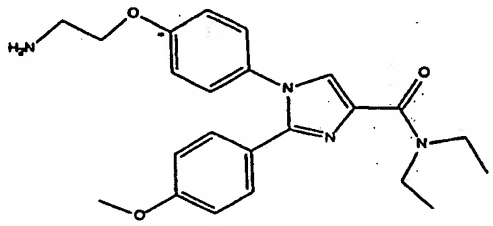
m.p. 93-94 ℃

NMR (DMSO-d6) d; 1.14 (6H,d, J=6.8Hz), 3.31-3.40 (2H, m), 3.59-3.66 (1H, m), 3.84 (3H, s), 4.00 (2H, t, J=5.4Hz), 5.53 (2H, s), 6.18 (1H, t, J=5.4Hz), 6.82 (1H, d, J=8.7Hz), 7.05(2H, d, J=8.9Hz), 7.34 (2H, d, J=8.9Hz), 8.65 (1H, dd, J=8.7Hz, 2.3Hz), 8.09 (1H, d, J=2.3Hz), 8.18(1H, s).

IR (KBr): 3375, 3311, 3217, 3091, 2966, 2937, 2871, 1658, 1608 cm-1.

Mass m/e : 381 (M++1).

Example 317



(E0317)

E0317 was obtained in the similar manner that of E0313.

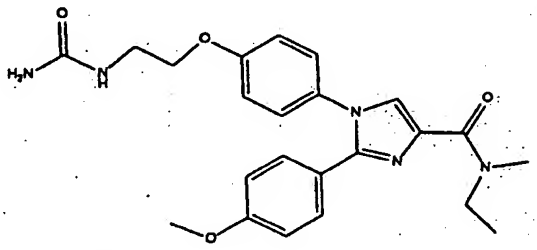
m.p. 108-109 ℃

NMR (DMSO-d6) d; 1.03-1.30 (6H, m), 1.46-1.76 (2H, br), 2.88 (2H, t, J=5.7Hz), 3.17-3.50 (2H, m), 3.74 (3H, s), 3.80-4.07 (2H, m), 3.95 (2H, t, J=5.7Hz), 6.89 (2H, d, J=8.8Hz), 7.02 (2H, d, J=8.8Hz), 7.26 (4H, d, J=8.8Hz), 7.71 (1H, s).

IR (KBr): 3458., 3425, 3390, 3365, 2972, 2933, 2887, 1604 cm-1.

Mass m/e : 409 (M++1).

Example 318



(E0318)

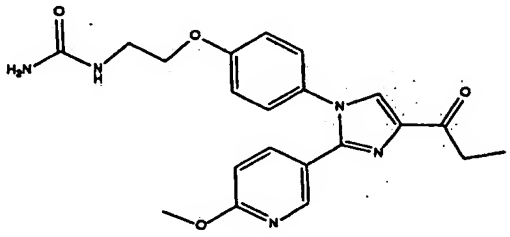
Triethylamine (16 ml) and trimethylsillilisocyanate (74 ml) was added to a solution of E0313 (80 mg) in CH2Cl2 (2 ml) under stirring at 0℃. After stirring at 0℃ for 1 hour, the reaction mixture was poured into 1N aqueous hydrogen chloride and stirred at room temperature for 5 minutes. Then the mixture was alkalinised with saturated sodium hydrogen carbonate and extracted with ethyl acetate, dried over MgSO4 and evaporated in vacuo. The resulting precipitates were corrected by filtration and washed with diisopropyl ether to give E0318 (6 mg).

NMR (DMSO-d6) d; 1.10-1.28 (5H, m), 2.89-3.00 (2H, m), 3.40-3.53 (2H, m), 3.74 (3H, s), 3.98-4.08(1H, m), 3.98 (2H, t, J=5.7 Hz), 5.54 (2H, s), 6.55 (1H, s), 6.89 (2H, d, J=8.8Hz), 7.03 (2H, d, J=8.9Hz), 7.26 (4H, d, J=8.8Hz), 7.72 (1H, s).

IR (KBr): 3431, 3359, 3290, 3275, 3240, 2960, 2925, 2856, 1734, 1697, 1649, 1614 cm-1.

Mass m/e : 438 (M++1).

Example 319



(E0319)

E0319 was obtained in the similar manner that of E0318.

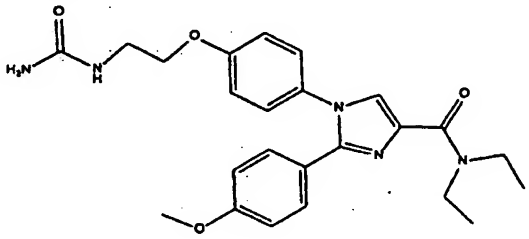
m.p. 109-111 ℃

NMR (DMSO-d6) d; 1.10 (3H, t, J=7.3Hz), 2.95 (2H, q, J=7.3Hz), 3.84 (3H, s), 3.99 (2H, t, J=5.5Hz), 5.54 (2H, s), 6.18 (1H, t, J=5.6Hz), 6.81 (1H, d, J=8.6Hz), 7.05 (2H, d, J=8.9Hz), 7.33 (2H, d, J=8.8Hz), 7.65 (1H, dd, J=8.6Hz, 2.3Hz), 8.09 (1H, d, J=2.3Hz), 8.17 (1H, s), 11.09 (2H, br).

IR (KBr): 3444, 3217, 3039, 2885, 2831, 2783, 1772, 1722, 1610 cm-1.

Mass m/e : 410 (M++1).

Example 320



(E0320)

E0320 was obtained in the similar manner that of E0318.

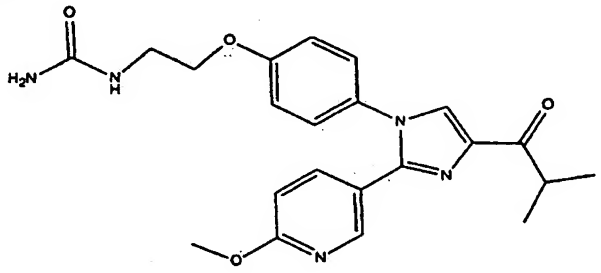
m.p. 167-169 ℃

NMR (DMSO-d6) d; 1.10-1.30 (6H, m), 3.28-3.56 (4H, m), 3.74 (3H, s), 3.82-3.98 (2H, m), 3.97 (2H, t, J=5.4Hz), 5.54 (2H, s), 6.18 (1H, t, J=5.4Hz), 6.89 (2H, d, J=8.9Hz), 7.03 (2H, d, J=8.9Hz), 7.26 (4H, d, J=8.8Hz), 7.71 (1H, s).

IR (KBr): 3406, 3359, 3232, 2970, 2935, 2879, 2837, 1680 cm-1.

Mass m/e : 452 (M++1).

Example 321



(E0321)

E0321 was obtained in the similar manner that of E0318.

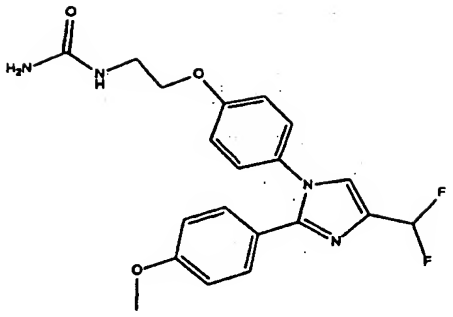
m.p. 170-172 ℃

NMR (DMSO-d6) d; 1.14 (6H,d, J=6.9Hz), 3.33-3.43 (2H, m), 3.57-3.60 (1H, m), 3.84 (3H, s), 4.00 (2H, t, J=5.6Hz), 5.54 (2H, s), 6.18 (1H, t, J=5.6Hz), 6.82 (1H, d, J=8.7Hz), 7.05 (2H, d, J=8.9Hz), 7.34 (2H, d, J=8.9Hz), 7.65 (1H, dd, J=8.7Hz, 2.3Hz), 8.09 (1H, d, J=2.3Hz), 8.18 (1H, s).

IR (KBr): 3473, 3390, 3338, 3089, 3026, 2969, 2877, 1662, 1606 cm-1.

Mass m/e : 424 (M++1).

Example 322

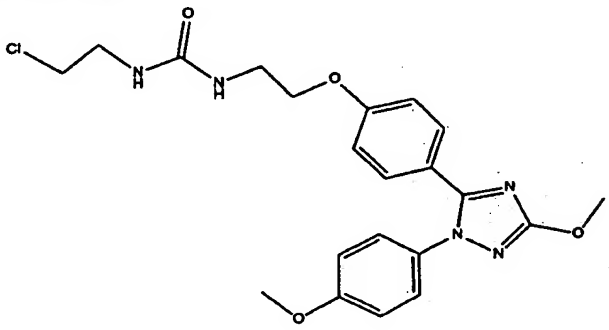


(E0322)

E0322 was obtained according to a similar manner to that of E0318.

MS (ESI, m/e) 403(M+1)

Example 323

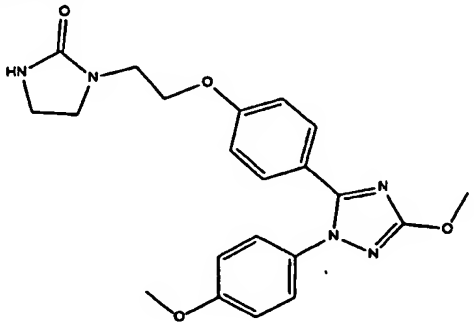


(E0323)

2-Chloroethyl isocyanate (124 mg, 1.32 mmol) was added to a solution of E0070 (200 mg, 0.881 mmol) in 1 ml of toluene. The mixture was stirred for 15 minutes at room temperature. An insoluble material was isolated by filtration, washed with toluene, and dried in vacuo (250 mg, 95.4% yield) to give E0323.

MS (ESI, m/e) 446(M+1)

Example 324

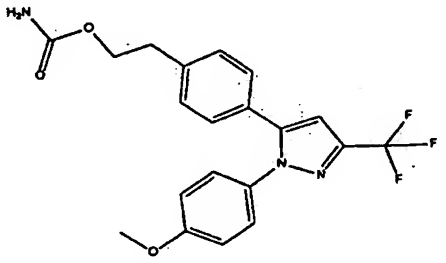


(E0324)

Under ice-bath cooling, sodium hydride (60% dispersion, 19.7 mg, 0.493 mmol) was added to a solution of E0323 (200 mg, 0.449 mmol) in tetrahydrofuran (0.8 ml) and N,N-dimethylformamide (0.8 ml). The mixture was stirred at room temperature for 2.5 hours. The mixture was quenched with water and extracted with chloroform (x2). The combined organic layers were washed with water and brine, dried over magnesium sulfate, and evaporated to give oil. The oil was purified with column chromatography (SiO2 10 g, eluted with ethyl acetate, 50% ethyl acetate / acetone and acetone). The desired product E0324 was washed with isopropylether, isolated by filtration, and dried in vacuo (56 mg, 30.5% yield).

1H NMR (CDCl3, ppm) d 3.32-3.49(2H, m), 3.51-3.70(4H, m), 3.85(3H, s), 4.05(3H, s), 4.07-4.19(2H, m), 4.45(1H, bs), 6.75-6.89(2H, m), 6.90-7.00(2H, m), 7.20-7.36(2H, m), 7.37-7.50(2H, m),
MS (ESI, m/e) 410(M+1)

Example 325



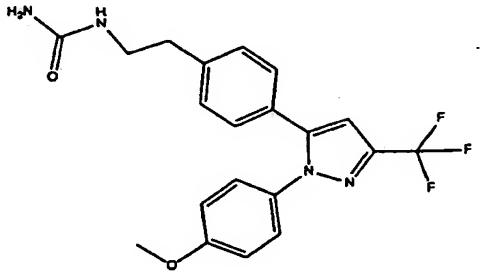
(E0325)

Trichloroacetyl isocyanate 62.4mg was added to a solution of E0014 100mg in CH2Cl2 2ml under ice bath cooling. After stirring at ambient temperature for 3hours, the reaction mixture was concentrated in vacuo. The residue was dissolved in THF 1ml, MeOH 1ml, and H2O 1ml. Potassium carbonate 153mg was added to the reaction mixture, and stirred at ambient temperature overnight. The reaction mixture was partitioned between AcOEt and H2O. The organic layer was washed with saturated aqueous sodium chloride solution, dried over magnesium sulfate, and concentrated in vacuo. The residual solid was recrystallized from AcOEt-n-hexane to give E0325 84.1mg as a white powder.

mp. 169-170℃
IR (KBr) : 3435, 3332, 3263, 3209, 1684, 1610, 1516cm-1
Mass (ESI+) : 406 (M+H)+

400MHz 1H NMR (DMSO-d6, d) : 2.84(2H, t, J=6.8 Hz), 3.79(3H, s), 4.10(2H, t, J=6.8 Hz), 6.30-6.70(2H, br), 7.00(2H, d, J=9.0 Hz), 7.14(1H, s), 7.21(2H, d, J=8.4 Hz), 7.26(2H, d, J=8.4 Hz), 7.29(2H, d, J=9.0 Hz)

Example 326



(E0326)

Trimethylisocyanate 42.7mg was added to a solution of E0055 98.2mg and triethylamine 30mg in CH2Cl2 1ml under ice bath cooling. The reaction mixture was stirred at same temperature for 1hour and concentrated in vacuo. The residue was purified by preparative thin layer silica gel chromatography developed by MeOH / CHCl3 = 10%. The separated silica gel was extracted with 10% MeOH/CHCl3, filtered, and the solvent was evaporated in vacuo. The residue was crystallized from ethylacetate-diisopropyl ehter to give E0326 (59.7mg) as a white powder.

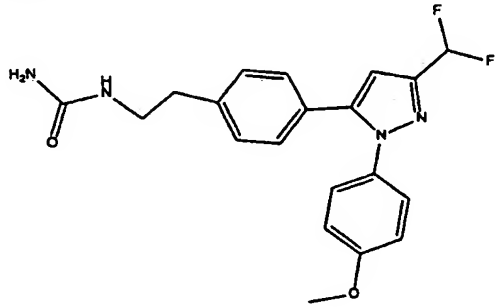
mp.157-158℃

IR (KBr) : 3406, 3357, 3330, 3209, 1704, 1662, 1614, 1529, 1520cm-1

Mass (ESI+) : 405 (M+H)+

200MHz 1H NMR (DMSO-d6, d) NO06.067: 2.62-2.70(2H, m), 3.13-3.24(2H, m), 3.79(3H, s), 5.42(2H, s), 5.93(1H, t, J=5.4 Hz), 7.00(2H, d, J=8.8 Hz), 7.12(1H, s), 7.21(4H, s), 7.29(2H, d, J=8.8 Hz)

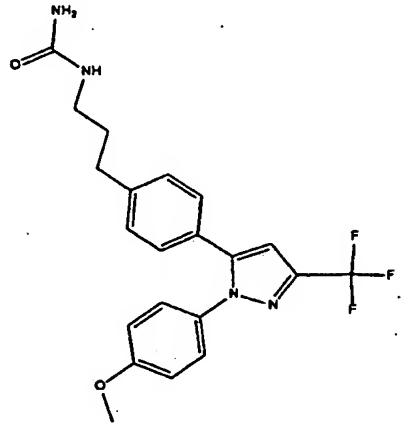
Example 327



(E0327)

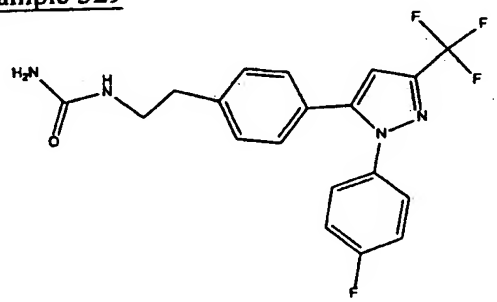
This compound was obtained according to a similar manner to that of E0326.
IR (film): 3343.9, 1656.6, 1604.5, 1550.5, 1515.8, 1457.9, 1342.2, 1251.6, 1029.8 cm-1.

Example 328



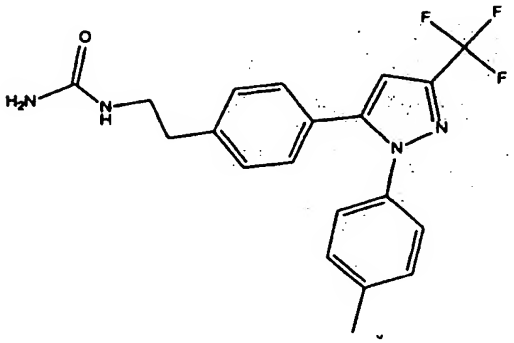
(E0328)
This compound was obtained according to a similar manner to that of E0326.
IR (film): 3345.9, 1654.6, 1604.5, 1556.3, 1513.9, 1465.6, 1240.0, 1160.9, 1132.0cm-1.

Example 329



(E0329)
This compound was obtained according to a similar manner to that of E0326.
IR (film): 3345.9, 1658.5, 1602.6, 1552.4, 1236.2, 1159.0, 1133.9cm-1.

Example 330

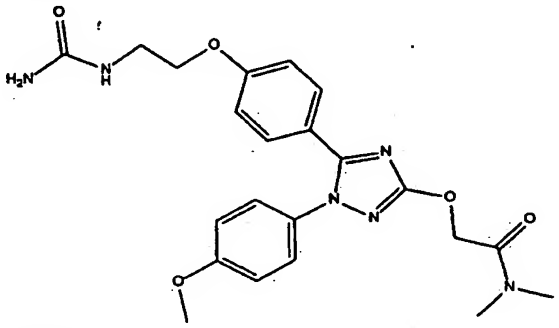


(E0330)

This compound was obtained according to a similar manner to that of E0326.

IR(film): 3345.9, 1658.5, 1602.6, 1552.4, 1517.7, 1236.2, 1159.0, 1133.9cm-1.

Example 331



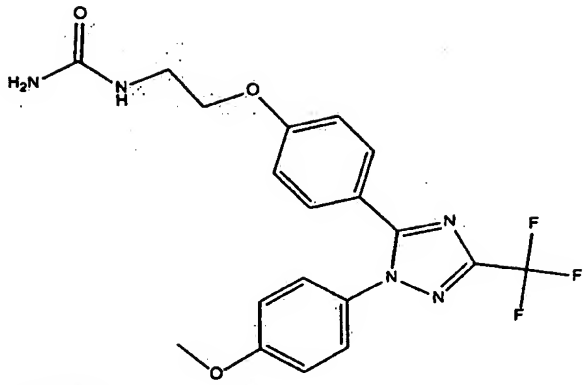
(E0331)

E0331 was obtained according to a similar manner to that of E0326.

1H NMR (DMSO-d6, ppm) d 2.84(3H, s), 2.96(3H, s), 3.25-3.40(2H, m), 3.80(3H, s), 3.95(2H, t, J=5.5 Hz), 5.00(2H, s), 5.52(2H, s), 6.15(1H, bt, J=5.6 Hz), 6.89-7.08(4H, m), 7.21-7.39(4H, m),

MS (ESI, m/e) 455(M+1)

Example 332



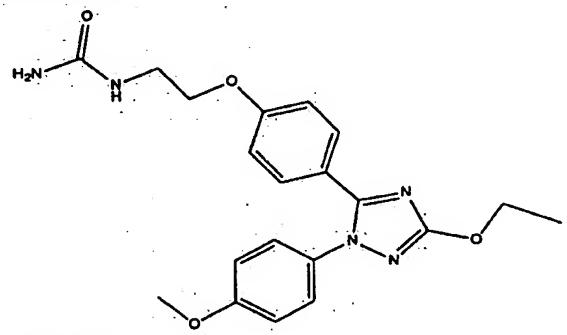
(E0332)

E0332 was obtained according to a similar manner to that of E0326.

1H NMR (CDCl3, ppm) d 3.60(2H, bq, J=5.3 Hz), 3.87(3H, s), 4.05(2H, bt, J=4.9 Hz), 4.38(2H, bs), 4.82-5.00(1H, m), 6.84(2H, d, J=8.8 Hz), 6.96(2H, d, J=8.9 Hz), 7.30(2H, d, J=9.0 Hz), 7.46(2H, d, J=8.9 Hz),

MS (ESI, m/e) 422(M+1)

Example 333



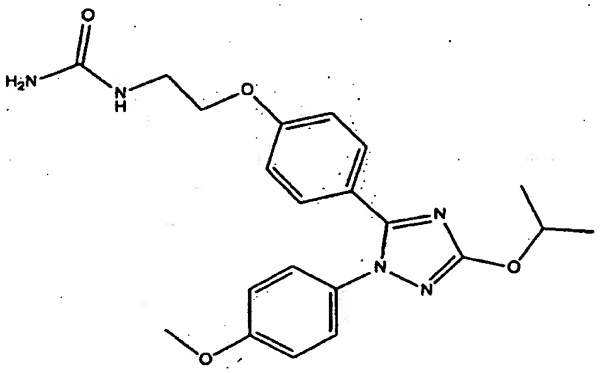
(E0333)

E0333 was obtained according to a similar manner to that of E0326.

1H NMR (DMSO-d6, ppm) d 1.35(3H, t, J=7.0 Hz), 3.28-3.39(2H, m), 3.80(3H, s), 3.95(2H, t, J=5.5 Hz), 4.29(2H, q, J=7.0 Hz), 5.52(2H, s), 6.15(1H, bt, J=5.5 Hz), 6.89-7.07(4H, m), 7.25-7.39(4H, m),

MS (ESI, m/e) 398(M+1)

Example 334



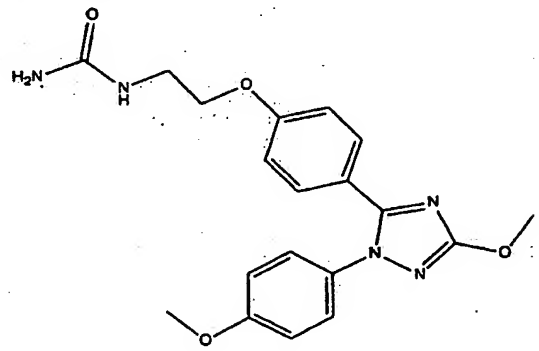
(E0334)

E0334 was obtained according to a similar manner to that of E0326.

1H NMR (CDCl3, ppm) d 1.42(6H, d, J=6.2 Hz), 3.55(2H, q, J=5.3 Hz), 3.84(3H, s), 3.97(2H, t, J=5.1 Hz), 4.57(2H, bs), 5.01(1H, 7th, J=6.1 Hz), 5.36(1H, bt, J=5.9 Hz), 6.76(2H, d, J=8.8 Hz), 6.84-7.00(2H, m), 7.17-7.35(2H, m), 7.35-7.49(2H, m),

MS (ESI, m/e) 412(M+1)

Example 335



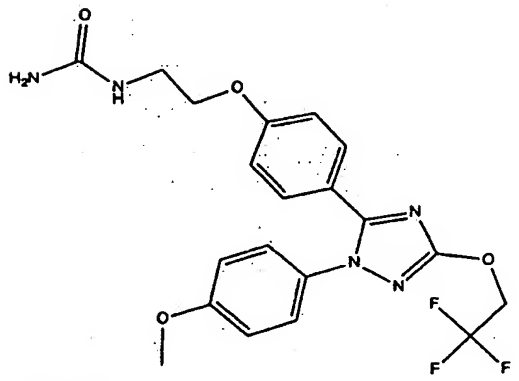
(E0335)

E0335 was obtained according to a similar manner to that of E0326.

1H NMR (CDCl3, ppm) d 3.55(2H, q, J=5.4 Hz), 3.84(3H, s), 3.96(2H, t, J=5.1 Hz), 4.04(3H, s), 4.66(2H, bs), 5.51(1H, bt, J=5.7 Hz), 6.68-6.83(2H, m), 6.85-7.00(2H, m), 7.17-7.30(2H, m), 7.30-7.47(2H, m),

MS (ESI, m/e) 384(M+1)

Example 336



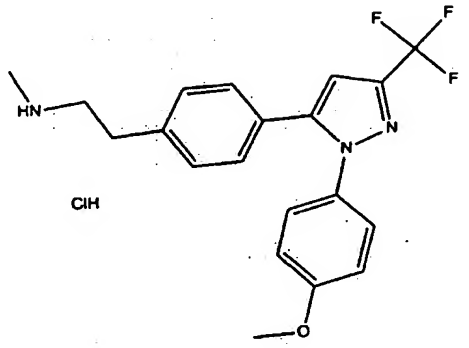
(E0336)

E0336 was obtained according to a similar manner to that of E0326.

1H NMR (DMSO-d6, ppm) d 3.20-3.41(2H, m), 3.81(3H, s), 3.95(2H, t, J=5.5 Hz), 4.99(2H, q, J=8.9 Hz), 5.52(2H, bs), 6.15(1H, bt, J=5.5 Hz), 6.90-7.10(4H, m), 7.28-7.42(4H, m),

MS (ESI, m/e) 452(M+1)

Example 337

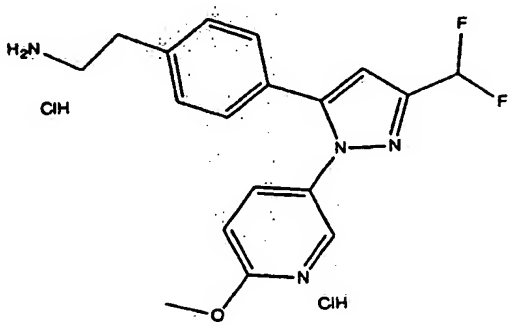


(E0337)

A mixture of E0078 (150mg) and 6ml of 4N HCl/dioxane was stirred at room temperature. After 2 hours, the reaction mixture was evaporated under reduced pressure to give 128mg (quant.) of E0337 as an oil.

IR(film): 3403.7, 1513.9, 1467.6, 1241.9, 1162.9, 1130.1cm-1.

Example 338

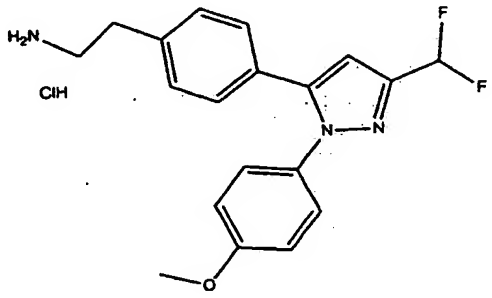


(E0338)

This compound was obtained according to a similar manner to that of E0337.

IR(film): 3428.8, 1662.34, 1612.2, 1500.4, 1461.8, 1390.4, 1292.1, 1166.7, 1087.7, 1029.8cm-1.

Example 339

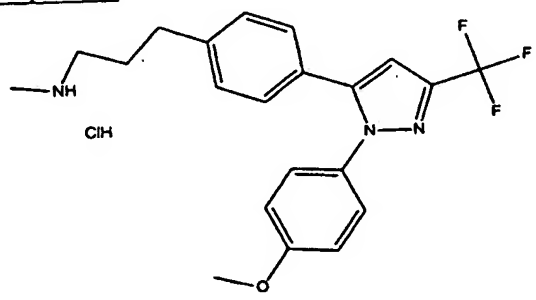


(E0339)

This compound was obtained according to a similar manner to that of E0337.

IR (film): 3403.74, 2965.98,1610.27, 1513.85, 1461.78, 1251.58, 1170.58, 1085.73, 1029.80, 836.955, 800.314 cm-1.

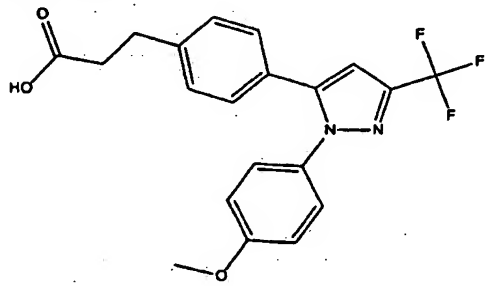
Example 340



(E0340)

This compound was obtained according to a similar manner to that of E0337.
IR (film): 3432.7, 1511.9, 1467.6, 1240.0, 1160.9, 1130.1cm-1.

Example 341

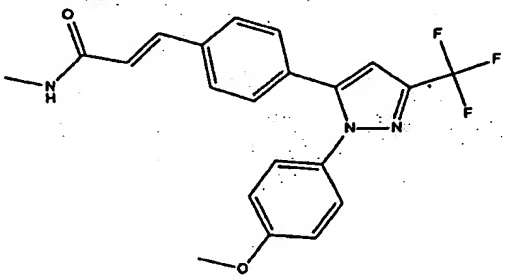


(E0341)

A mixture of E0163 (100mg) and Pd/C (100mg) in EtOH (10m) was stirred under H2 atmosphere for 3.0 hours. After filtration, a filtrate was evaporated under reduced pressure. The resudue was dissolved in EtOH and filtered with syringe driven filter, and evaporated to give 93mg (93%) of E0341.

IR (film):3019.9, 1704.8, 1513.9, 1303.6, 1238.1, 1133.9cm-1.

Example 342

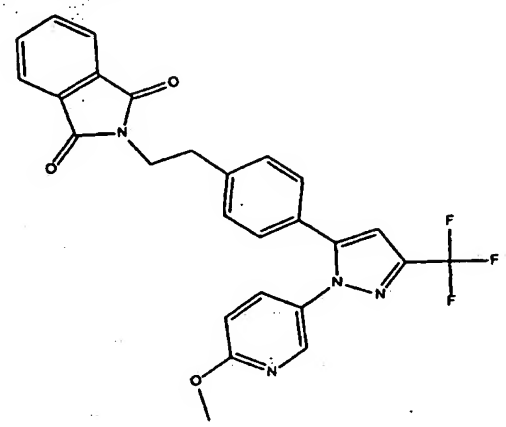


(E0342)

T a suspension of E0163 (200mg) in toluene (4ml) was added thionylchloride (0.19ml) at room temperature. The reaction mixture was stirred at 100oC for 5 hours until the mixture become clear solution. After then, the mixture was evaporated under reduced pressure. (become solid) THF was added, and then aqueous MeNH2 (37%) was added. The mixture was stirred for 1 hour, and quenched with water, and extracted twice with EtOAc. The combined organic layer was washed with sat.NaHCO3, water and brine, dried over Na2SO4, filtered and evaporated under reduced pressure to give 63mg (31%) of E0342 as a powder.

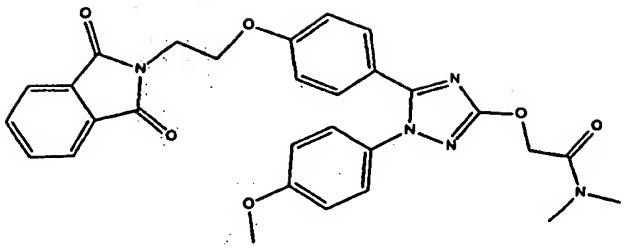
mp: 155-157℃
IR(film) 3297.7, 1662.3, 1617.9, 1513.9, 1236.2, 1162.9, 1133.9cm-1

Example 343



(E0343)
A suspension of E0353 (1.8 g) and potassium phtalimido (1.13 g) in N,N-dimethylformamide (6.6 ml) was stirred at 80℃ for 3 hours. The mixture was added water (700 ml) and extracted with a mixture of ethyl acetate and hexane (2:1) (x4). The combined organic layers were washed with aqueous sodium hydroxide (1N) (x2) and brine, dried over magnesium sulfate, and evaporated to give oil, which was purified with column chromatography (SiO2 100 ml, eluted with 30% ethyl acetate/hexane) to give oil (1.83g, 91.1%). Ethanol (15 ml) was added to the oil, then the mixture was stirred at room temperature for 10 minutes. The precipitate was filtered, washed with ethanol (3 ml), and dried under reduced pressure to give E0343 as a white solid (1.16 g, 58%).
NMR(CDCl3), 3.00(2H, t, J=7.6 Hz), 3.93(2H, t, J=7.6 Hz), 3.94(3H, s), 6.73(1H, s), 6.73(1H, d, J=8.7 Hz), 7.13-7.26(4H, m), 7.49(1H, dd, J=8.7, 2.5 Hz), 7.70-7.86(4H, m), 8.10(1H, d, J=2.5 Hz).
MS(ESI+), 515(M+Na).

Example 344

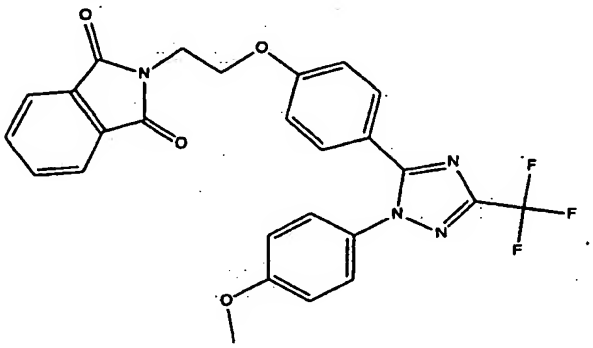


(E0344)

E0344 was obtained according to a similar manner to that of E0343 (650 mg, 82.9% yield).

1H NMR (CDCl3, ppm) d 2.99(3H, s), 3.06(3H, s), 4.03-4.15(2H, m), 4.15-4.28(2H, m), 4.99(2H, s), 6.70-6.82(2H, m), 6.82-6.97(2H, m), 7.17-7.30(2H, m), 7.30-7.42(2H, m), 7.68-7.80(2H, m), 7.80-7.91(2H, m),
MS (ESI, m/e) 542(M+1)

Example 345

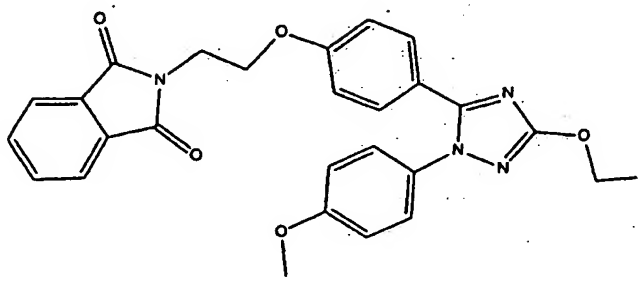


(E0345)

E0345 was obtained according to a similar manner to that of E0343 (582 mg, 69.8% yield).

1H NMR (DMSO-d6, ppm) d 3.82(3H, s), 3.96(2H, bt, J=5.7 Hz), 4.24(2H, bt, J=5.7 Hz), 6.94(2H, d, J=8.9 Hz), 7.07(2H, d, J=9.0 Hz), 7.35-7.55(4H, m), 7.75-7.98(4H, m),
MS (ESI, m/e) 509(M+1)

Example 346



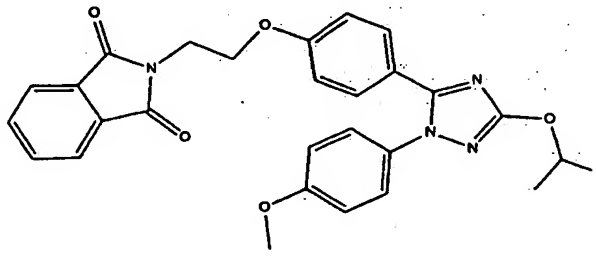
(E0346)

E0346 was obtained according to a similar manner to that of E0343 (1.55 g, 92.5% yield).

1H NMR (CDCl3, ppm) d 1.44(3H, t, J=7.0 Hz), 3.83(3H, s), 4.04-4.17(2H, m), 4.17-4.28(2H, m), 4.38(2H, q, J=7.0 Hz), 6.70-6.83(2H, m), 6.85-6.95(2H, m), 7.17-7.30(2H, m), 7.31-7.42(2H, m), 7.68-7.79(2H, m), 7.80-7.94(2H, m),

MS (ESI, m/e) 485(M+1)

Example 347



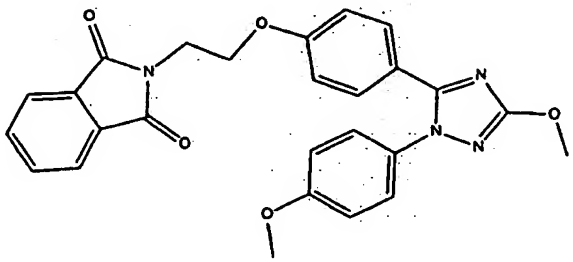
(E0347)

E0347 was obtained according to a similar manner to that of E0343 (542 mg, 59.3% yield).

1H NMR (CDCl3, ppm) d 1.42(6H, d, J=6.1 Hz), 3.83(3H, s), 4.07-4.19(2H, m), 4.19-4.29(2H, m), 5.01(1H, 7th, J=6.1 Hz), 6.71-6.84(2H, m), 6.85-6.97(2H, m), 7.18-7.30(2H, m), 7.31-7.45(2H, m), 7.69-7.80(2H, m), 7.80-7.91(2H, m),

MS (ESI, m/e) 499(M+1)

Example 348



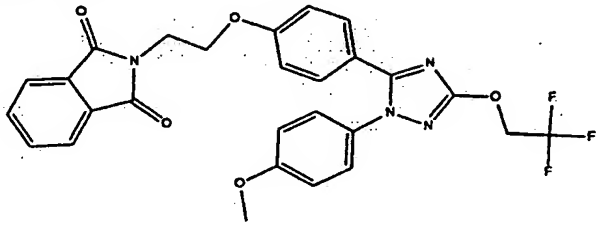
(E0348)

E0348 was obtained according to a similar manner to that of E0343 (540 mg, 58% yield).

1H NMR (CDCl3, ppm) d 3.83(3H, s), 4.03(3H, s), 4.03-4.29(4H, m), 6.72-6.87(2H, m), 6.87-6.99(2H, m), 7.19-7.32(2H, m), 7.33-7.45(2H, m), 7.68-7.80(2H, m), 7.80-7.92(2H, m),

MS (ESI, m/e) 471(M+1)

Example 349



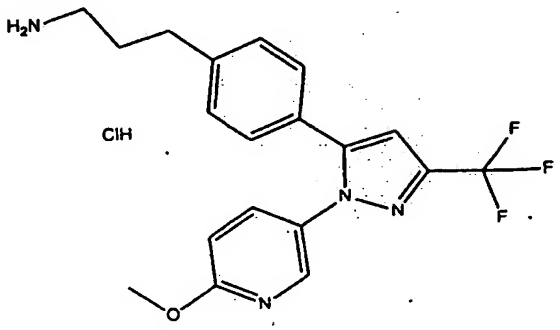
(E0349)

E0349 was obtained according to a similar manner to that of E0343 (1.1 g, 81.6% yield).

1H NMR (CDCl3, ppm) d 3.84(3H, s), 4.10(2H, t, J=5.2 Hz), 4.22(2H, t, J=4.9 Hz), 4.73(2H, q, J=8.4 Hz), 6.76-6.85(2H, m), 6.85-6.99(2H, m), 7.24(2H, dd, J=2.4,7.0 Hz), 7.38(2H, d, J=6.7 Hz), 7.67-7.95(4H, m),

MS (ESI, m/e) 539(M+1)

Example 350



(E0350)

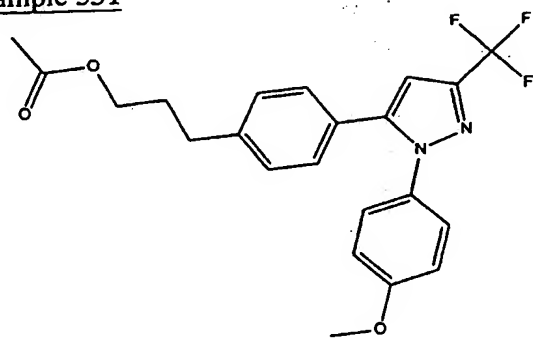
6M HCl 0.045ml was added to a solution of E0065 (101.5mg) in AcOEt 1ml and EtOH 1ml. The mixture was concentrated and dried in vacuo to give E0350 (94.8mg) as an amorphous powder.

IR (neat) : 3433, 3020, 2956, 1668, 1658, 1612, 1572, 1543, 1500cm-1

Mass (ESI+) : 377 (M+H)+

200MHz 1H NMR (DMSO-d6, d) : 1.76-1.92(2H, m), 2.52-2.81(4H, m), 3.88(3H, s), 6.93(1H, d, J=8.9 Hz), 7.19(1H, s), 7.26(4H, s), 7.76(1H, dd, J=8.9,2.7 Hz), 8.19(1H, d, J=2.7 Hz)

Example 351

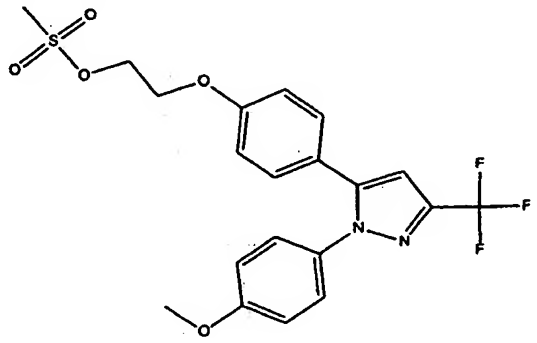


(E0351)

To a mixture of P0002 (5.0g) and CF3COOEt (3.5ml) in DMF (30ml) was added NaH (1.1g) under ice-cooling. The reaction mixture was allowed to warm to room temperature, and stirred under 40oC for 1 hour. The reaction mixture was extracted twice with EtOAc. The organic layer was washed with water and brine, dried over MgSO4, filtered and evaporated under reduced pressure. The residue, sodium acetate (2.23g) and 4-methoxyphenylhydrazine (3.96g) in acetic acid (20ml) was stirred at room temperature for 15 hours. The mixture was extracted twice with ethyl acetate. The combined organic layer was washed with water (twice), sat.NaHCO3, water and

brine, dried over MgSO4, filtered and evaporated under reduced pressure. The residue was column chromatographed on silica gel (Hex/EtOAc = 8:1-4:1) to give 2.58g (36%) of E0351 as an oil.

Example 352

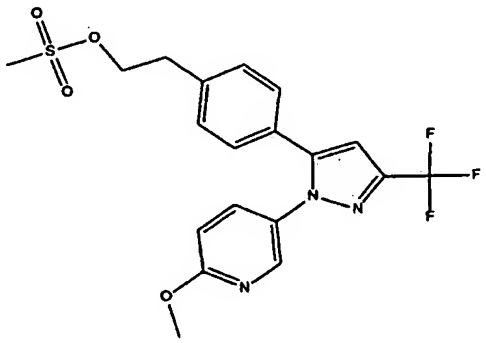


(E0352)

To a solution of E0223 (326.7 mg) in ethyl acetate (3 ml) was added methanesulfonyl chloride (86.9 ml) and triethylamine (0.181 ml) at 0℃. After stirring for 40 minutes at 0℃, the mixture was quenched with water and extracted with ethyl acetate (x3). The combined organic layers were washed with water and brine, dried over sodium sulfate, and evaporated under reduced pressure to give E0352 as an oil (351.3 mg, 89%).

NMR(CDCl3); 3.09(3H, s), 3.82(3H, s), 4.22-4.26(2H, m), 4.52-4.59(2H, m), 6.68(1H, s), 6.75(2H, d, J=8.7 Hz), 6.87(2H, d, J=8.9 Hz), 7.16(2H, d, J=8.7 Hz), 7.22(2H, d, J=8.9 Hz).

Example 353

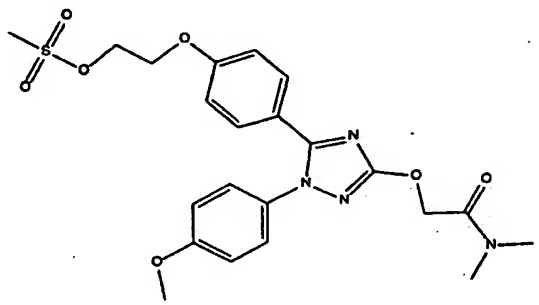


(E0353)

This compound was obtained according to a similar manner to that of E0352 as a pale

yellow oil (1.82 g, 98.6%).
NMR(CDCl3), 2.91(3H, s), 3.07(2H, t, J=6.8 Hz), 3.94(3H, s), 4.43(2H, t, J=6.8 Hz), 6.75(1H, s), 6.78(1H, d, J=8.2 Hz), 7.17-7.26(4H, m), 7.58(1H, dd, J=9.0, 2.9 Hz), 8.05(1H, d, J=2.8 Hz).
MS(ESI+), 442.1(MH+), 464.0(M+Na).

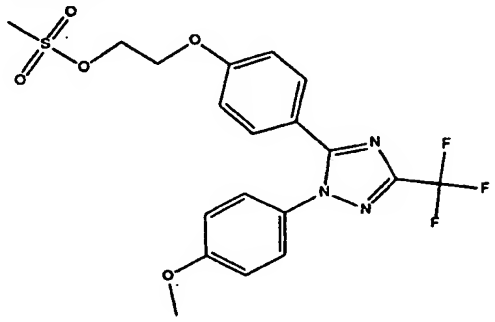
Example 354



(E0354)
E0354 was obtained according to a similar manner to that of E0353 (710 mg, 92.6% yield).

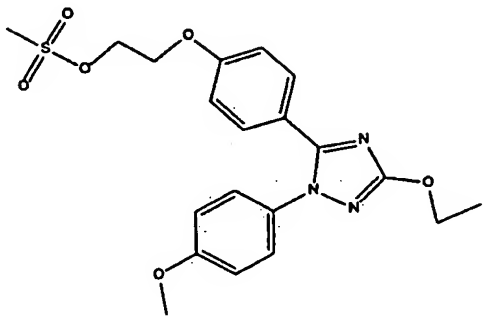
MS (ESI, m/e) 491(M+1)

Example 355



(E0355)
E0355 was obtained according to a similar manner to that of E0353 (750 mg, 111.1% yield).
MS (ESI, m/e) 458(M+1)

Example 356

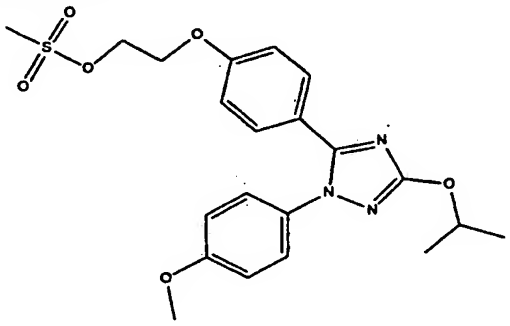


(E0356)

E0356 was obtained according to a similar manner to that of E0353 (1.62 g, 109% yield).

MS (ESI, m/e) 434(M+1)

Example 357

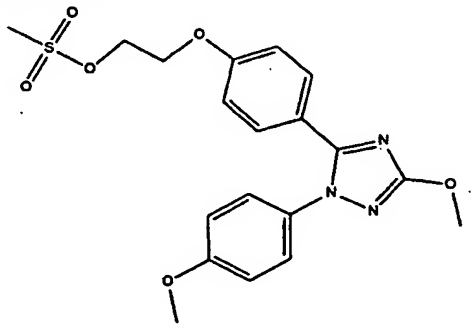


(E0357)

FR275741 was obtained according to a similar manner to that of E0353 (820 mg, 104.1% yield).

MS (ESI, m/e) 448(M+1)

Example 358

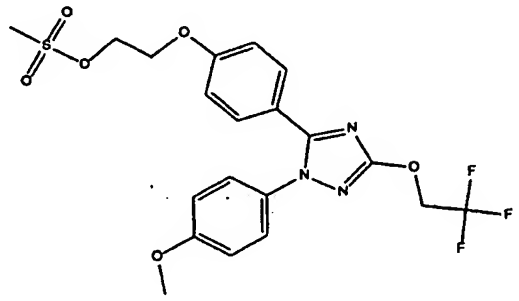


(E0358)

E0358 was obtained according to a similar manner to that of E0353 (831 mg, 104% yield).

MS (ESI, m/e) 420(M+1)

Example 359

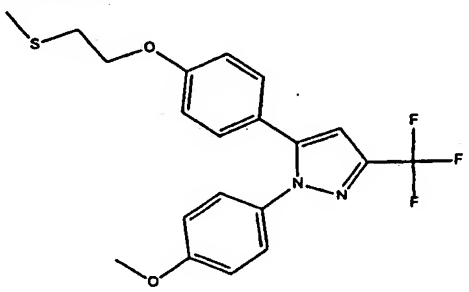


(E0359)

E0359 was obtained according to a similar manner to that of E0353 (1.22 g, 120.5% yield).

MS (ESI, m/e) 488(M+1)

Example 360



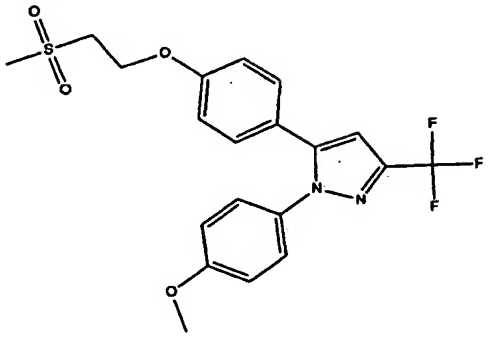
(E0360)

A suspension of E0352 (351.3 mg) and sodium thiomethoxide (162 mg) in N,N-dimethylformamide (3 ml) was stirred at 60℃ for 3.5 hours. The mixture was quenched with water and extracted with ethyl acetate (x3). The combined organic layers were washed with water and brine, dried over magnesium sulfate, and evaporated to give oil. The oil was purified with column chromatography (SiO2 50 ml, eluted with 10% ethyl acetate / hexane) to give E0360 as an oil (236.7 mg, 75.3%).

NMR(CDCl3); 2.24(3H, s), 2.88(2H, t, J=6.6 Hz), 3.82(3H, s), 4.15(2H, t, J=6.6 Hz), 6.67(1H, s), 6.83(2H, d, J=8.8 Hz), 6.88(2H, d, J=9.0 Hz), 7.13(2H, d, J=8.8 Hz),

7.23(2H, d, J=9.0 Hz).
MS(ESI+);431(M+Na).

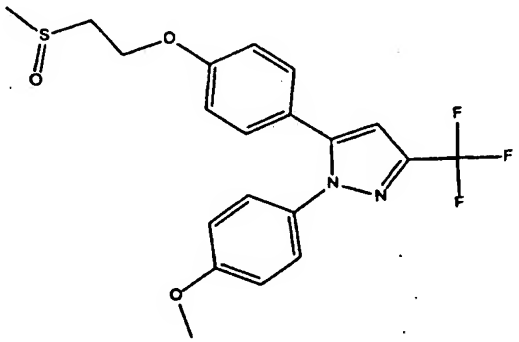
Example 361



(E0361)

To a solution of E0360 (103.5 mg) in dichloromethane (1 ml) was added m-chloroperbenzoic acid (134 mg) at room temperature. After stirring at room temperature for 1 hour, the mixture was added saturated sodium hydrogen sulfate aqueous solution (0.5 ml) and sodium thiosulfate pentahydrate (100 mg), and stirred for 30 minutes at room temperature. The mixture was filtered by Chemelut 1001(Varian) and evaporated to give oil, which was purified with preparative TLC (1 mm, 50% ethyl acetate/hexane) to give E0361 as an amorphous (105.9 mg, 94.9%).
NMR(CDCl3);3.07(3H, s), 3.45(2H, t, J=5.3 Hz), 4.44(2H, t, J=5.3 Hz), 3.83(3H, s), 6.69(1H, s), 6.69-6.90(4H, m), 7.15-7.26(4H, m).
MS(ESI+); 463.1 (M+Na)+. IR(KBr, 20727-8), 1612.2, 1515.8cm-1.

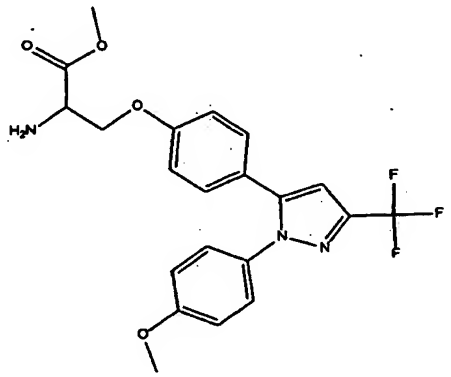
Example 362



(E0362)

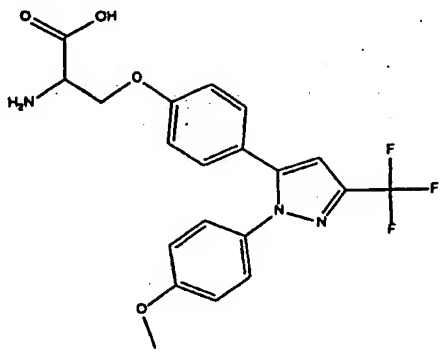
To a solution of E0360 (104.8 mg) in dichloromethane (1 ml) was added m-chloroperbenzoic acid (44.7 mg) at 0℃, and the mixture was stirred at 0℃ for 1 hour. Then m-chloroperbenzoic acid (35 mg) was added to the mixture. After stirring at 0℃ for 30 minutes, the mixture was quenched with saturated sodium hydrogen sulfate aqueous solution (0.5 ml) and sodium thiosulfate pentahydrate (100 mg), and stirred for 30 minutes at room temperature. The mixture was filtered by Chemelut 1001(Varian) and evaporated to give oil, which was purified with preparative TLC (1 mm, ethyl acetate) to give 2 fractions of E0361 (TLC upper) as an amorphous (40.7 mg, 37.4%) and E0362 (TLC lower) as a powder (60 mg, 55%).
NMR(CDCl3); 2.70(3H, s), 2.99-3.27(2H, m), 3.83(3H, s), 4.40-4.46(2H, m), 6.68(1H, s), 6.84-6.90(4H, m), 7.15(2H, d, J=8.7 Hz), 7.22(2H, d, J=9.0 Hz).
MS(ESI+); 447.1 (M+Na).
IR(KBr); 1612.2, 1513.9cm-1.

Example 363



(E0363)
To a solution of E0191 (500 mg) in dichloromethane (1.5 ml) was added successively anisol (0.5 ml) and triflutoroacetic acid (1 ml). After stirring at room temperature for 2 hours, the mixture was quenched with saturated sodium hydrogen carbonate aqueous solution and extracted with ethyl acetate (x3). The organic layers were dried over magnesium sulfate and evaporated to give oil, which was purified with column chromatography (SiO2 50 ml, eluted with ethyl acetate) to give E0363 as an oil (302.5 mg, 94.2%).
NMR(CDCl3), 3.77(3H, s), 3.80(3H, s), 3.80-3.87(1H, m), 4.21-4.28(2H, m), 6.67(1H, s), 6.80-6.89(4H, m), 7.13(2H, d, J=8.7 Hz), 7.22(2H, d, J=8.9 Hz).
MS(ESI+), 436.1(MH+).

Example 364



(E0364)

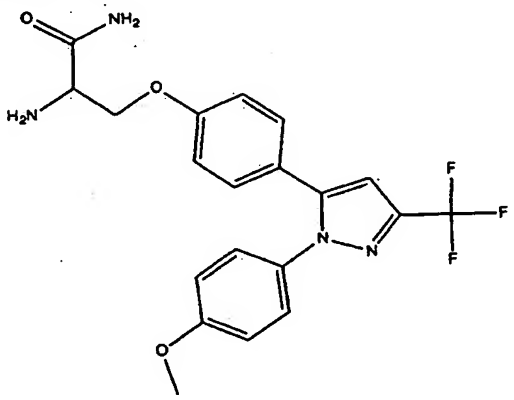
A solution of E0363 (104.6 mg) in methanol (3 ml) and sodium hydroxide aqueous solution (1N, 2 ml) was stirred at room temperature for 3 hours. The mixture was evaporated, and methanol was added to the residue and evaporated to give white powder, which was purified with preparative TLC (1 mm, 20%methanol/chloroform) to give E0364 as a powder (29.9 mg, 29.5%).

NMR(DMSO-d6), 3.50-3.54(1H, m), 3.79(3H, s), 4.13-4.30(2H, m), 6.91-7.07(5H, m), 7.21(2H, d, J=8.7 Hz), 7.27(2H, d, J=8.9 Hz).

MS(ESI-).420.4(M-H).

IR(KBr), 1641, 1616cm-1.

Example 365

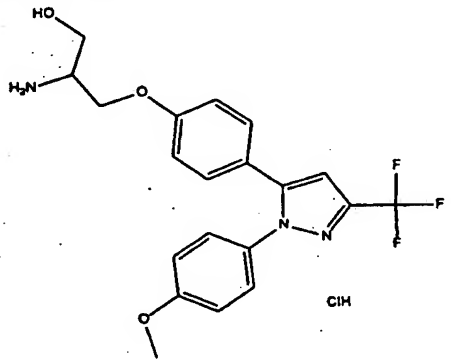


(E0365)

To a solution of E0363 (106.6 mg) in methanol (2 ml) was added concentrated ammonia solution (1 ml). After stirring at room temperature overnight, the mixture was

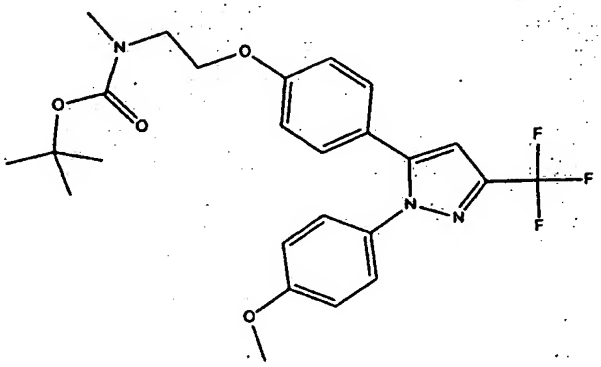
evaporated to give solid, which was purified with preparative TLC (1 mm, 20%methanol/chloroform) to give E0365 as a solid (58.2 mg, 56.5%).
NMR(CDCl3), 3.75-3.82(1H, m), 3.82(3H, s), 4.15-4.29(2H, m), 6.67(1H, s), 6.83-6.91(4H, m), 7.14(2H, d, J=6.7 Hz), 7.22(2H, d, J=9.0 Hz).
MS(ESI+).421.4(MH+), 462.4(MHMeCN)+.
IR(KBr), 1658 cm-1.

Example 366



(E0366)
To a solution of E0363 (87.5 mg) in tetrahydrofuran (1 ml) was added lithium aluminum hydride (30.5 mg) at room temperature. After stirring at room temperature for 2 hours, the mixture was quenched with water (30 ml), sodium hydroxide aqueous solution (15%, 30 ml), and water (90 ml), and then stirred at room temperature for 30 minutes. Magnesium sulfate and celite was added to the mixture, then the suspension was filtered and washed with tetrahydrofuran.
The filtrate was evaporated to give oil, which was purified with preparative TLC (0.5 mm, 20%methanol/chloroform) to give oil.
To a solution of the oil in ethyl acetate was added a solution of hydrogen chloride in ethyl acetate (4N, 0.5 ml), and then the mixture was evaporated to give E0366 as an oil (43.5 mg, 49%).
NMR(CDCl3), 3.64-4.13(5H, m), 3.76(3H, s), 6.60(1H, s), 6.73-6.85(4H, m), 7.07(2H, d, J=8.5 Hz), 7.16(2H, d, J=8.9 Hz).
MS(ESI+), 408.1(MH+)(Free). IR(Neat, 20727-5), 1614.1cm-1.

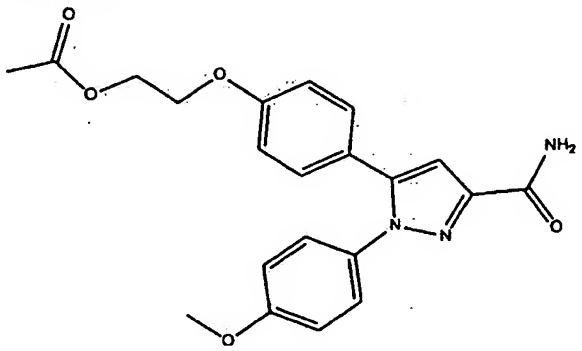
Example 367



(E0367)

To a suspension of sodium hydride (34.8 mg) in terahydrofuran (2 ml) was added a solution of E0258 (208 mg) in tetrahydrofuran (1 ml) at 0℃, and then the mixture was stirred at room temperature for 20 minutes. Then iodomethane (54.2 ml) was added to the mixture. After stirring at room temperature overnight, the mixture was quenched with water, extracted with ethyl acetate (x3). The combined organic layers were washed with water (x3) and brine, dried over magnesium sulfate, and evaporated under reduced pressure to give oil, which was purified with preparative TLC (1 mm, 30% ethyl acetate/hexane) to give E0368 as an oil (160 mg, 74.7%).
NMR(CDCl3), 1.45(9H, s), 2.97(3H, s), 3.59(2H, t, J=5.5 Hz), 3.82(3H, s), 4.0-4.15(2H, m), 6.67(1H, s), 6.80-6.91(4H, m), 7.13(2H, d, J=8.8 Hz), 7.23(2H, d, J=9.0 Hz).
MS(ESI+).514.2(M+Na).

Example 368

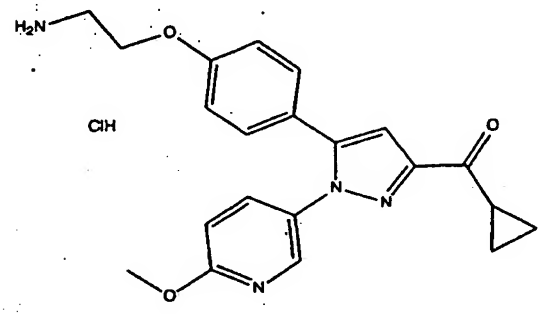


(E0368)

AcCl 0.31ml was added to a suspension of E0258 (1.29g) and Et3N 0.66ml in CH2Cl2 10ml under ice bath cooling. The mixture was stirred at ambient temperature for 2hours. AcCl 0.31ml and Et3N 0.66ml was added and stirred at ambient temperature for 3hours.

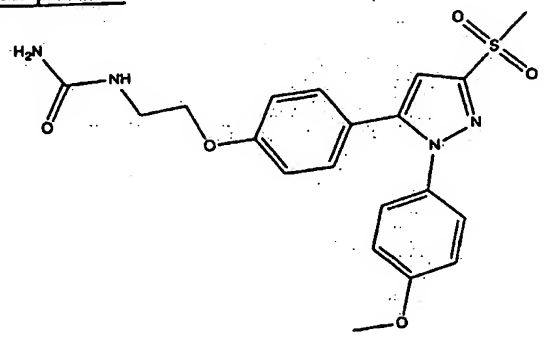
To this mixture was added H2O and stirred at ambient temperature for a while. White precipitates were appeared, which was collected and washed with H2O and diisopropyl ether to give E0368 (879.3mg) as a white powder.
Mass (ESI+) : 396(M+H)+
200MHz 1H NMR (DMSO-d6, d) : 2.03(3H, s), 3.78(3H, s), 4.15-4.19(2H, m), 4.29-4.33(2H, m), 6.89(1H, s), 6.93(2H, d, J=8.8 Hz), 6.98(2H, d, J=8.9 Hz), 7.17(2H, d, J=8.8 Hz), 7.26(2H, d, J=8.9 Hz), 7.32(1H, s), 7.63(1H, s)

Example 369



(E0369)
To a solution of E0285 (61.4mg) in CH2Cl2 2ml was added trimethylsilyl trifluoromethanesulfonate 85.6mg at 0℃, followed by an addition of triethylamine 39mg. The mixture was stirred at 0℃ for 30minutes, and partitioned between AcOEt and H2O. The organic layer was washed with saturated aqueous sodium chloride solution, dried over magnesium sulfate, and concentrated in vacuo. The residue was purified by preparative thin layer silica gel chromatography developed by 28% NH3aq : MeOH : CHCl3 =1:10:100. The separated silica gel was extracted with 28% NH3aq : MeOH : CHCl3 =1:10:100 and the solvent was evaporated in vacuo. The residu was dried under vacuo and then dissolved in EtOH 3ml. To this solution was added 1M HCl 0.0892ml and concentrated in vacuo. The residue was dried under vacuo to give E0369 (37mg) as an amorphous powder.
IR (KBr) : 2958, 1668, 1662, 1612, 1581, 1568, 1549, 1531, 1500cm-1
Mass (ESI+) : 379 (M+H)+
200MHz 1H NMR
1.05(4H, d, J=6.2 Hz), 3.04(1H, m), 3.15-3.24(2H, m), 3.89(3H, s), 4.16-4.22(2H, m), 6.94(1H, d, J=8.8 Hz), 7.00(2H, d, J=8.7 Hz), 7.02(1H, s), 7.27(2H, d, J=8.7 Hz), 7.78(1H, dd, J=2.7,8.8 Hz), 8.14(2H, brs), 8.21(1H, d, J=2.7 Hz)

Example 370



(E0370)

To a solution of 2-{4-[1-(4-methoxyphenyl)-3-(methylsulfonyl)-1H-pyrazol-5-yl]phenoxy}ethanamine (133mg,0.342mmol) in methylene chloride(5ml) was added trimethylsilyl isocyanate (118mg,1.03mmol) and triethylamine(1.39mg,1.37mmol) at ambient temperature and stirred for two days. The reaction mixture was washed with water and brine , dried over magnesium sulfate, filtered and evaporated. Purification by column chromatography (silica gel, methylene chloride/methanol=20/1) followed by recrystallization from ethyl acetate gave 102 mg (69%) of E0370 as white crystals.

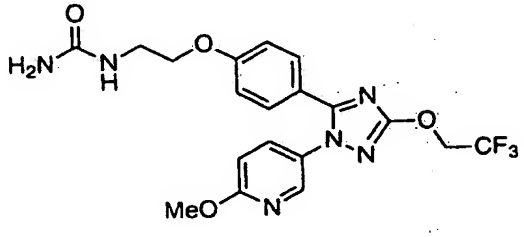
mp.165-167℃

Mass;431(M+1)

IR(KBr);1650,1310CM-1

NMR(DMSO-d6,δ); 3.32(2H, q, J=5.5 Hz), 3.33(3H, s), 3.79(3H, s), 3.94(2H, t, J=5.5 Hz), 5.52(2H, s), 6.14(1H, t, J=5.5 Hz), 6.94(2H, d, J=8.7 Hz), 7.01(2H, d, J=8.9 Hz), 7.11(1H, s), 7.20(2H, d, J=8.7 Hz), 7.28(2H, d, J=8.9 Hz),

Example 371



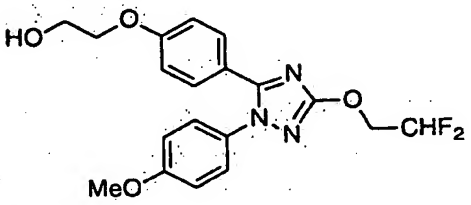
(E0371)

To a solution of P0064 in dimethylformamide (1 ml), potassium carbonate (453 mg, 3.28 mmol), potassium iodide (90 mg, 0.546 mmol) and N-(2-bromoethyl)urea (274 mg, 1.64 mmol) were added. The mixture was heated at 120℃ for 3 hours. Then

N-(2-bromoethyl)urea (91 mg, 54 mmol) was added to the mixture per 1 hour at 5 times. After cooling, ethyl acetate and water were poured into the mixture. The organic layer was separated and dried over magnesium sulfate. The solvent was removed under reduced pressure. The residue was purified by silicagel chromatografy (dichloromethane-methanol 20:1). The desired product E0371 was isolated by filtration ,washed with isopropylether and dried in vacuo. (100 mg, 40.5% yield)

1H NMR (DMSO-d6, ppm) d 3.22-3.47(2H, m), 3.90(3H, s), 3.96(2H, t, J=5.5 Hz), 5.01(2H, q, J=8.8 Hz), 5.53(2H, bs), 6.16(1H, bt, J=5.5 Hz), 6.91-7.08(3H, m), 7.39(2H, d, J=8.7 Hz), 7.82(1H, dd, J=8.8, 2.7 Hz), 8.26(1H, d, J=2.5 Hz),
MS (ESI, m/e) 353(M+1)

Example 372

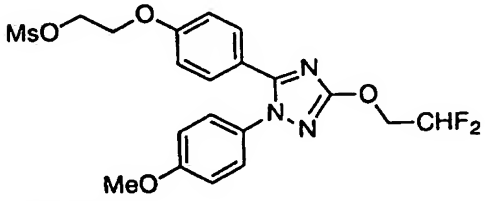


(E0372)

E0372 was obtained according to a similar manner to that of E0200(1.52 g, 95% yield).

1H NMR (CDCl3, ppm) d 2.09(1H, t, J=6.2 Hz), 3.85(3H, s), 3.90-4.01(2H, m), 4.05-4.13(2H, m), 4.54(2H, dt, J=13.1,4.4 Hz), 6.18(1H, tt, J=55.2,4.4 Hz), 6.79-7.00(4H, m), 7.22-7.31(2H, m), 7.35-7.49(2H, m),
(ESI, m/e) 392(M+1)

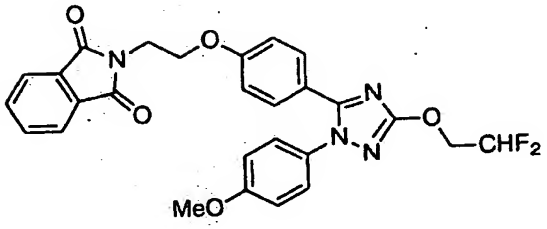
Example 373



(E0373)
E0373 was obtained according to a similar manner to that of E0353 (1.49 g, 124.2%

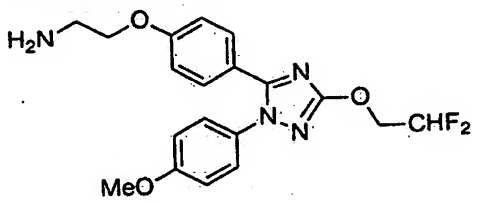
yield).
MS (ESI, m/e) 470(M+1)

Example 374



(E0374)
E0374 was obtained according to a similar manner to that of E0343 (1.06 g, 79.7% yield).
1H NMR (CDCl3, ppm) d 3.84(3H, s), 4.05-4.17(2H, m), 4.18-4.29(2H, m), 4.53(2H, td, J=13.0,4.3 Hz), 6.19(2H, tt, J=55.3,4.4 Hz), 6.75-6.88(2H, m), 6.89-6.99(2H, m), 7.18-7.32(2H, m), 7.32-7.45(2H, m), 7.65-7.80(2H, m), 7.80-7.90(2H, m),
MS (ESI, m/e) 521(M+1)

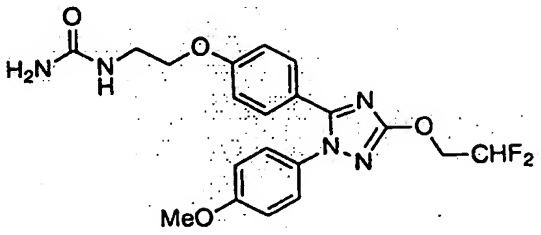
Example 375



(E0375)
E0375 was obtained according to a similar manner to that of E0062 (721 mg, 100.1% yield).

1H NMR (CDCl3, ppm) d 3.08(2H, t, J=5.2 Hz), 3.85(3H, s), 3.99(2H, t, J=5.1 Hz), 4.54(2H, td, J=13.1,4.3 Hz), 6.18(1H, tt, J=55.2,4.3 Hz), 6.77-6.89(2H, m), 6.89-7.00(2H, m), 7.21-7.32(2H, m), 7.35-7.49(2H,),
MS (ESI, m/e) 391(M+1)

Example 376

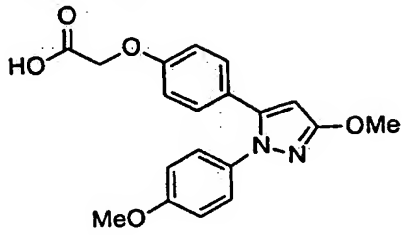


(E0376)

To a solution of E0375 (200 mg, 0.512 mmol) in 1 ml of EtOH and 4 ml of 1N-HCl, potassium cyanate (208 mg, 2.56 mmol) was added slowly. The mixture was stirred at 50° C for 1hr. Furthermore, potassium cyanate (124 mg, 1.54 mmol) was added and stirred at same temperature for 1hr. After cooling, water and 1N-HCl were added and an insoluble material was isolated by filtration. The residue was purified by recrystallized with EtOH (1 ml) to get the white crystal of E0376 (160mg, 72.1%).

1H NMR (DMSO-d6, ppm) d 3.19-3.39(2H, m), 3.81(3H, s), 3.95(2H, bt, J=5.5 Hz), 4.56(2H, td, J=14.9,3.4 Hz), 5.52(2H, bs), 6.43(2H, tt, J=54.2,3.4 Hz), 6.09-6.23(1H, m), 6.90-7.11(4H, m), 7.27-7.41(4H, m),
MS (ESI, m/e) 434(M+1)

Example 377



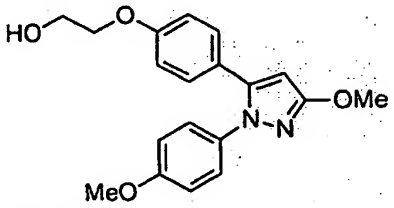
(E0377)

A solution of P0078 64mg in DMF 1ml was added 60% NaH 11.4mg at 4℃ and the mixture was stirred at same temperature for 30minutes. To the mixture was added bromoacetic acid 33mg and the mixture was stirred at ambient temperature for 2hours. The reaction was quenched by adding 1M HCl 2ml, and the mixture was extracted with AcOEt. The organic layer was washed with H2O, sat.aqNaCl, dried over MgSO4, concentrated in vacuo to give E0377 (73mg) as crystals.

Mass (ESI+) : 355 (M+H)+

200MHz 1H NMR (DMSO-d6, d) : 3.79(3H, s), 3.96(3H, s), 4.63(2H, s), 5.88(1H, s), 6.82(4H, d, J=9.0 Hz), 7.14(2H, d, J=9.0 Hz), 7.17(2H, d, J=9.0 Hz)

Example 378



(E0378)

Boron trifluoride diethyl etherate 137mg was added to a suspension of sodium borohydride 29.3mg in THF 3ml with cooling in an ice bath, and the mixture was stirred at same temperature for 30minutes. To the reaction mixture was added E0377 (137mg) in THF 3ml in one portion and the mixture was stirred at ambient temperature for 4hours. The reacion was quenched by adding ice water containing 1M HCl 1ml, and the mixture was stirred at ambient temperature for 1hour. The mixture was extracted with AcOEt for 2 times, the combined organic layers were washed with sat.aqNaHCO3, sat.aqNaCl, dried over MgSO4, evaporated in vacuo. The residue was purified by preparative thin layer chromatography developed with AcOEt / n-hexane = 50%. The residue was crystallized from IPE to give E0378 (79.2mg) as a white powder.

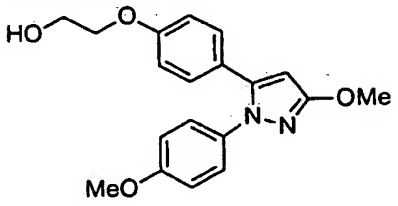
mp. 107-109℃

IR (KBr) : 3334, 2935, 1693, 1612, 1564, 1520cm-1

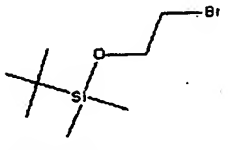
Mass (ESI+) : 341 (M+H)+

200MHz 1H NMR (DMSO-d6, d) : 2.02(1H, t, J=6.1 Hz), 3.80(3H, s), 3.91-3.99(2H, m), 3.97(3H, s), 4.04-4.09(2H, m), 5.88(1H, s), 6.82(4H, d, J=9.0 Hz), 7.14(2H, d, J=9.0 Hz), 7.17(2H, d, J=9.0 Hz)

Example 379



(E0379)



(E0379-0)

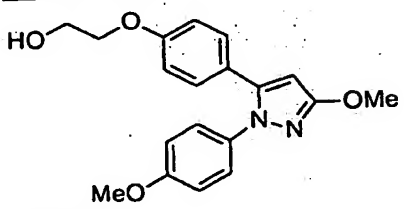
To a solution of P0078 (237mg) in DMF 2ml was added 60% NaH 41.6mg with cooling in an ice bath, and the mixture was stirred at ambient temperature for 1hour.

To the mixture was added E0379-0 (287mg) in DMF 1ml and the mixture was stirred at ambient temperature for 13hours, and at 60℃ for 3hours. The reaction was quenched by adding sat.NH4Claq, and the mixture was extracted with AcOEt. The organic layer was washed with H2O, sat.aqNaCl, dried over MgSO4, concentrated in vacuo. The residue was dissolved in EtOH 4ml, and conc.HCl 40 μ L was added. After stirring at ambient temperature for 2hours, the mixture was concentrated in vacuo. The residue was partitioned between AcOEt and sat.aqNaHCO3, and the organic layer was washed with sat.aqNaCl, dried over MgSO4, concentrated in vacuo. The residue was purified by silica gel column chromatography eluted with AcOEt / n-hexane = 40%, 60%. The residue was crystallized from AcOEt 1ml and IPE 2ml. The obtained crystals were recrystallized from AcOEt 0.7ml and IPE 1.5ml to give E0379 (196.9mg) as white crystals.

mp. 114.9-116 (115)℃ Mass (ESI+) : 341 (M+H)+

200MHz 1H NMR (DMSO-d6, d) : 3.65-3.73(2H, m), 3.75(3H, s), 3.83(3H, s), 3.94-3.99(2H, m), 4.86(1H, t, J=5.4 Hz), 6.04(1H, s), 6.87-6.96(4H, m), 7.10-7.16(4H, m)

Example 380



(E0380)

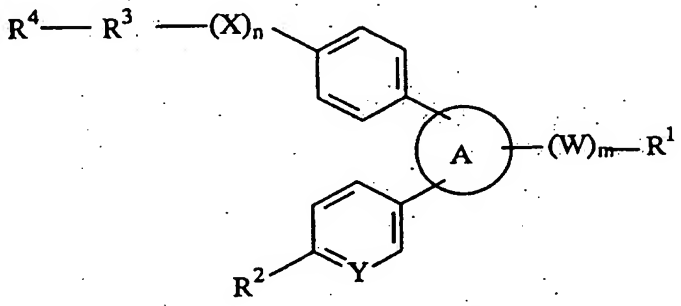
To a solution of P0078 (100mg) in DMF 1ml was added 60% NaH 17.5mg with cooling in an ice bath. The mixture was stirred at ambient temperature for 1hour. The mixture was cooled to 0℃. To the mixture was added 2-bromoethyl acetate 113mg and the mixture was stirred at ambient temperature for 24hours. The reaction was quenched by adding sat.NH4Claq, and the mixture was extracted with AcOEt. The organic layer was washed with H2O, sat.aqNaCl, dried over MgSO4, concentrated in vacuo. The residue was dissolved in THF 0.9ml and MeOH 0.9ml. To this solution was added 1M NaOH 0.4ml. The mixture was stirred at ambient temperature for 1hour. The mixture was partitioned between AcOEt and H2O, and the aqueous layer was reexracted with AcOEt. The combined organic layers were washed with sat.aqNaCl, dried over MgSO4, concentrated in vacuo. The residue was crystallized from AcOEt 0.3ml-IPE 0.9ml to give E0380 (82.4mg) as white crystals.

Mass (ESI+) : 341 (M+H)+

Throughout this specification and the claims which follow, unless the context requires otherwise, the word "comprise", and variations such as "comprises" and "comprising", will be understood to imply the inclusion of a stated integer or step or group of integers or steps but not the exclusion of any other integer or step or group of integers or steps.

THE CLAIMS DEFINING THE INVENTION ARE AS FOLLOWS:

1. A compound of the formula (I):



(I)

wherein R1 is lower alkyl which is optionally substituted with suitable substituent(s), cyclo(lower)alkyl, lower alkynyl, cyano, acyl, heterocyclic group, or N,N-di(lower)alkylcarbamoyl;

R2 is lower alkyl, lower alkoxy, cyano or 1H-pyrrol-1-yl;

R3 is lower alkylene or lower alkenylene;

R4 is hydroxy, protected hydroxy, amino, protected amino, carboxy, protected carboxy, acyl, or cyano;

X is O, S, SO or SO2;

Y is CH or N;

W is O, S, SO or SO2;

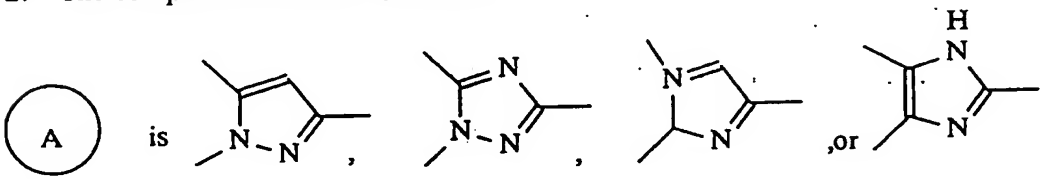
m is 0 or 1;

n is 0 or 1; and

is a N-containing heterocyclic group;

or salts thereof.

2. The compound of Claim 1, wherein



3. A pharmaceutical composition comprising the compound (I) or its salts of Claim 1, as an active ingredient, in association with a pharmaceutically non-toxic carrier or excipient.

4. A compound of Claim 1 for use as a medicament

5. A method for treatment and/or prevention of inflammatory conditions, various pains, collagen diseases, autoimmune diseases, various immunity diseases, analgesic, thrombosis, cancer or neurodegerative diseases which comprises administering an effective amount of the compound or its salts of Claim 1 to human beings or animals.

6. Use of the compound of Claim 1 for the manufacture of a medicament for treatment and/or prevention of inflammatory conditions, various pains, collagen diseases, autoimmune diseases, various immunity diseases, analgesic, thrombosis, cancer or neurodegerative diseases in human beings or animals.

7. The analgesic agent comprising the compound of Claim 1, which is usable for treating and/or preventing pains caused by or associated with acute or chronic inflammations without causing gastrointestinal disorders.

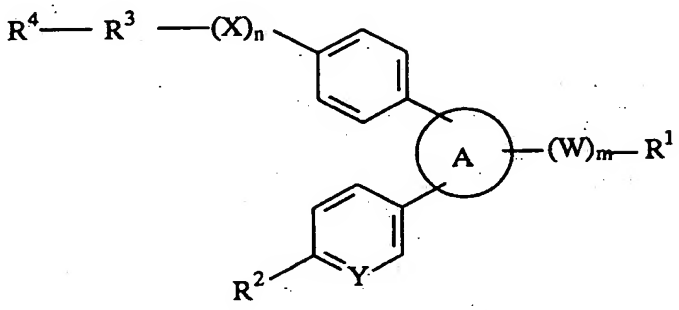
8. The analgesic agent of Claim 7, which is usable for treating or preventing pains caused by or associated with rheumatoid arthritis, osteoarthritis, lumbar rheumatism, rheumatoid spondylitis, gouty arthritis, or juvenile arthritis; lumbago; cervico-omo-brachial syndrome; scapulohumeral periarthritis; pain and tumescence after operation or injury without causing gastrointestinal disorders.

9. A commercial package comprising the pharmaceutical composition containing the compound (I) identified in Claim 1 and a written matter associated therewith, wherein the written matter states that the compound (I) can or should be used for preventing or treating inflammatory conditions, various pains, collagen diseases, autoimmune diseases, various immunity diseases, analgesic, thrombosis, cancer or neurodegerative diseases.

DATED this 30th day of December, 2002
Fujisawa Pharmaceutical Co., Ltd.
By DAVIES COLLISON CAVE
Patent Attorneys for the Applicant

ABSTRACT

A compound of the formula (I):



(I)

wherein R1 is lower alkyl which is optionally substituted with suitable substituent(s), cyclo(lower)alkyl, lower alkynyl, cyano, acyl, heterocyclic group, or N,N-di(lower)alkylcarbamoyl;

R2 is lower alkyl, lower alkoxy, cyano or 1H-pyrrol-1-yl;

R3 is lower alkylene or lower alkenylene;

R4 is hydroxy, protected hydroxy, amino, protected amino, carboxy, protected carboxy, acyl, or cyano;

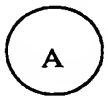
X is O, S, SO or SO2;

Y is CH or N;

W is O, S, SO or SO2;

m is 0 or 1;

n is 0 or 1; and

 is a N-containing heterocyclic group;

or salts thereof, which are useful as a medicament.